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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

(57) Abstract: Compositions and methods are disclosed for stimulating or inhibiting angiogenesis and/or cardiovascularization in mammals, including humans. Pharmaceutical compositions are based on polypeptides or antagonists thereto that have been identified for one or more of these uses. Disorders that can be diagnosed, prevented, or treated by the compositions herein include trauma such as wounds, various cancers, and disorders of the vessels including atherosclerosis and cardiac hypertrophy. In addition, the present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

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## COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

### 1. Field of the Invention

The present invention relates to compositions and methods useful for the modulation (*e.g.*, promotion or inhibition) of angiogenesis and/or cardiovascularization in mammals in need of such biological effect. The present invention further relates to the diagnosis and treatment of disorders involving angiogenesis (*e.g.*, cardiovascular as well as oncological disorders).

### 2. Background of the Invention

#### 2.1. Angiogenesis

Angiogenesis, defined as the growth or sprouting of new blood vessels from existing vessels, is a complex process that primarily occurs during embryonic development. Under normal physiological conditions in adults, angiogenesis takes place only in very restricted situations such as hair growth and wounding healing (Auerbach, W. and Auerbach, R., 1994, *Pharmacol Ther* 63(3):265-311; Ribatti et al., 1991, *Haematologica* 76(4):311-20; Risau, 1997, *Nature* 386(6626):671-4). Unregulated angiogenesis has gradually been recognized to be responsible for a wide range of disorders, including, but not limited to cardiovascular disease, cancer, rheumatoid arthritis, psoriasis and diabetic retinopathy (Folkman, 1995, *Nat Med* 1(1):27-31; Isner, 1999, *Circulation* 99(13):1653-5; Koch, 1998, *Arthritis Rheum* 41(6):951-62; Walsh, 1999, *Rheumatology (Oxford)* 38(2):103-12; Ware and Simons, 1997, *Nat Med* 3(2):158-64).

#### 2.2. Cardiac Disorders and Factors

Heart failure affects approximately five million Americans, and new cases of heart failure number about 400,000 each year. It is the single most frequent cause of hospitalization for people age 65 and older in the United States. Recent advances in the management of acute cardiac diseases, including acute myocardial infarction, are resulting in an expanding patient population that will eventually develop chronic heart failure. From 1979 to 1995, hospitalizations for congestive heart failure (CHF) rose from 377,000 to 872,000 (a 130 percent increase) and CHF deaths increased 116 percent.

CHF is a syndrome characterized by left ventricular dysfunction, reduced exercise tolerance, impaired quality of life, and markedly shortened life expectancy. The sine qua non of heart failure is an inability of the heart to pump blood at a rate sufficient to meet the metabolic needs of the body's tissues (in other words, there is insufficient cardiac output).

At least four major compensatory mechanisms are activated in the setting of heart failure to boost cardiac output, including peripheral vasoconstriction, increased heart rate, increased cardiac contractility, and increased plasma volume. These effects are mediated primarily by the sympathetic nervous system and the renin-angiotensin system. See, Eichhorn, American Journal of Medicine, 104: 163-169 (1998). Increased output from the

sympathetic nervous system increases vascular tone, heart rate, and contractility. Angiotensin II elevates blood pressure by 1) directly stimulating vascular smooth muscle contraction, 2) promoting plasma volume expansion by stimulating aldosterone and antidiuretic hormone secretion, 3) stimulating sympathetic-mediated vascular tone, and 4) catalyzing the degradation of bradykinin, which has vasodilatory and natriuretic activity. *See*, review by Brown and Vaughan, Circulation, 97: 1411-1420 (1998). As noted below, angiotensin II may also have directly deleterious effects on the heart by promoting myocyte necrosis (impairing systolic function) and intracardiac fibrosis (impairing diastolic and in some cases systolic function). *See*, Weber, Circulation, 96: 4065-4082 (1998).

A consistent feature of congestive heart failure (CHF) is cardiac hypertrophy, an enlargement of the heart that is activated by both mechanical and hormonal stimuli and enables the heart to adapt to demands for increased cardiac output. Morgan and Baker, Circulation, 83: 13-25 (1991). This hypertrophic response is frequently associated with a variety of distinct pathological conditions such as hypertension, aortic stenosis, myocardial infarction, cardiomyopathy, valvular regurgitation, and intracardiac shunt, all of which result in chronic hemodynamic overload.

Hypertrophy is generally defined as an increase in size of an organ or structure independent of natural growth that does not involve tumor formation. Hypertrophy of the heart is due either to an increase in the mass of the individual cells (myocytes), or to an increase in the number of cells making up the tissue (hyperplasia), or both. While the enlargement of an embryonic heart is largely dependent on an increase in myocyte number (which continues until shortly after birth), post-natal cardiac myocytes lose their proliferative capacity. Further growth occurs through hypertrophy of the individual cells.

Adult myocyte hypertrophy is initially beneficial as a short term response to impaired cardiac function by permitting a decrease in the load on individual muscle fibers. With severe, long-standing overload, however, the hypertrophied cells begin to deteriorate and die. Katz, "Heart Failure", in: Katz A.M. ed., Physiology of the Heart (New York: Raven Press, 1992) pp. 638-668. Cardiac hypertrophy is a significant risk factor for both mortality and morbidity in the clinical course of heart failure. Katz, Trends Cardiovasc. Med., 5: 37-44 (1995). For further details of the causes and pathology of cardiac hypertrophy *see, e.g.*, Heart Disease. A Textbook of Cardiovascular Medicine, Braunwald, E. ed. (W.B. Saunders Co., 1988), Chapter 14, "Pathophysiology of Heart Failure."

On a cellular level, the heart is composed of myocytes and surrounding support cells, generically called non-myocytes. While non-myocytes are primarily fibroblast/mesenchymal cells, they also include endothelial and smooth muscle cells. Indeed, although myocytes make up most of the adult myocardial mass, they represent only about 30% of the total cell numbers present in heart. In response to hormonal, physiological, hemodynamic, and pathological stimuli, adult ventricular muscle cells can adapt to increased workloads through the activation of a hypertrophic process. This response is characterized by an increase in myocyte cell size and contractile protein content of individual cardiac muscle cells, without concomitant cell division and activation of embryonic genes, including the gene for atrial natriuretic peptide (ANP). Chien *et al.*, FASEB J., 5: 3037-3046 (1991); Chien *et al.*, Annu. Rev. Physiol., 55: 77-95 (1993). An increment in myocardial mass as a result of an increase in myocyte size that is associated with an accumulation of interstitial collagen within the extracellular matrix and around intramyocardial coronary arteries has been described in left ventricular hypertrophy secondary to pressure overload



in humans. Caspari *et al.*, Cardiovasc. Res., **11**: 554-558 (1977); Schwarz *et al.*, Am. J. Cardiol., **42**: 895-903 (1978); Hess *et al.*, Circulation, **63**: 360-371 (1981); Pearlman *et al.*, Lab. Invest., **46**: 158-164 (1982).

It has also been suggested that paracrine factors produced by non-myocyte supporting cells may additionally be involved in the development of cardiac hypertrophy, and various non-myocyte derived hypertrophic factors, such as, leukocyte inhibitory factor (LIF) and endothelin, have been identified. Metcalf, Growth Factors, **2**: 169-173 (1992); Kurzrock *et al.*, Endocrine Reviews, **12**: 208-217 (1991); Inoue *et al.*, Proc. Natl. Acad. Sci. USA, **86**: 2863-2867 (1989); Yanagisawa and Masaki, Trends Pharm. Sci., **10**: 374-378 (1989); U.S. Patent No. 5,573,762 (issued November 12, 1996). Further exemplary factors that have been identified as potential mediators of cardiac hypertrophy include cardiotrophin-1 (CT-1) (Pennica *et al.*, Proc. Nat. Acad. Sci. USA, **92**: 1142-1146 (1995)), catecholamines, adrenocorticosteroids, angiotensin, and prostaglandins.

At present, the treatment of cardiac hypertrophy varies depending on the underlying cardiac disease. Catecholamines, adrenocorticosteroids, angiotensin, prostaglandins, LIF, endothelin (including endothelin-1, -2, and -3 and big endothelin), and CT-1 are among the factors identified as potential mediators of hypertrophy. For example, beta-adrenergic receptor blocking drugs (beta-blockers, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, carvedilol, etc.) and verapamil have been used extensively in the treatment of hypertrophic cardiomyopathy. The beneficial effects of beta-blockers on symptoms (*e.g.*, chest pain) and exercise tolerance are largely due to a decrease in the heart rate with a consequent prolongation of diastole and increased passive ventricular filling. Thompson *et al.*, Br. Heart J., **44**: 488-98 (1980); Harrison *et al.*, Circulation, **29**: 84-98 (1964). Verapamil has been described to improve ventricular filling and probably reducing myocardial ischemia. Bonow *et al.*, Circulation, **72**: 853-64 (1985).

Nifedipine and diltiazem have also been used occasionally in the treatment of hypertrophic cardiomyopathy. Lorell *et al.*, Circulation, **65**: 499-507 (1982); Betocchi *et al.*, Am. J. Cardiol., **78**: 451-457 (1996). However, because of its potent vasodilating properties, nifedipine may be harmful, especially in patients with outflow obstruction. Disopyramide has been used to relieve symptoms by virtue of its negative inotropic properties. Pollick, N. Engl. J. Med., **307**: 997-999 (1982). In many patients, however, the initial benefits decrease with time. Wigle *et al.*, Circulation, **92**: 1680-1692 (1995). Antihypertensive drug therapy has been reported to have beneficial effects on cardiac hypertrophy associated with elevated blood pressure. Examples of drugs used in antihypertensive therapy, alone or in combination, are calcium antagonists, *e.g.*, nitrendipine; adrenergic receptor blocking agents, *e.g.*, those listed above; angiotensin converting enzyme (ACE) inhibitors such as quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, and lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, and indapamide; and calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, and nicardipine.

For example, treatment of hypertension with diltiazem and captopril showed a decrease in left ventricular muscle mass, but the Doppler indices of diastolic function did not normalize. Szlachcic *et al.*, Am. J. Cardiol., **63**: 198-201 (1989); Shahi *et al.*, Lancet, **336**: 458-461 (1990). These findings were interpreted to indicate that excessive amounts of interstitial collagen may remain after regression of left ventricular hypertrophy. Rossi *et al.*, Am. Heart J., **124**: 700-709 (1992). Rossi *et al.*, *supra*, investigated the effect of captopril on the prevention and

regression of myocardial cell hypertrophy and interstitial fibrosis in pressure overload cardiac hypertrophy, in experimental rats.

Agents that increase cardiac contractility directly (ionotropic agents) were initially thought to benefit patients with heart failure because they improved cardiac output in the short term. However, all positive inotropic agents except digoxigenin have been found to result in increased long-term mortality, in spite of short-term improvements in cardiac performance. Massie, Curr. Op. in Cardiology, 12: 209-217 (1997); Reddy *et al.*, Curr. Opin. Cardiol., 12: 233-241 (1997). Beta-adrenergic receptor blockers have recently been advocated for use in heart failure. Evidence from clinical trials suggests that improvements in cardiac function can be achieved without increased mortality, though documented improvements of patient survival have not yet been demonstrated. See also, U.S. Pat. Nos. 5,935,924, 5,624,806; 5,661,122; and 5,610,134 and WO 95/28173 regarding the use of cardiotropin-1 or antagonists thereof, or growth hormone and/or insulin-like growth factor-I in the treatment of CHF. Another treatment modality is heart transplantation, but this is limited by the availability of donor hearts.

Endothelin is a vasoconstricting peptide comprising 21 amino acids, isolated from swine arterial endothelial culture supernatant and structurally determined. Yanagisawa *et al.*, Nature, 332: 411-415 (1988). Endothelin was later found to exhibit various actions, and endothelin antibodies as endothelin antagonists have proven effective in the treatment of myocardial infarction, renal failure, and other diseases. Since endothelin is present in live bodies and exhibits vasoconstricting action, it is expected to be an endogenous factor involved in the regulation of the circulatory system, and may be associated with hypertension, cardiovascular diseases such as myocardial infarction, and renal diseases such as acute renal failure. Endothelin antagonists are described, for example, in U.S. Pat. No. 5,773,414; JP Pat. Publ. 3130299/1991, EP 457,195; EP 460,679; and EP 552,489. A new endothelin B receptor for identifying endothelin receptor antagonists is described in U.S. Pat. No. 5,773,223.

Current therapy for heart failure is primarily directed to using angiotensin-converting enzyme (ACE) inhibitors, such as captopril, and diuretics. These drugs improve hemodynamic profile and exercise tolerance and reduce the incidence of morbidity and mortality in patients with CHF. Kramer *et al.*, Circulation, 67(4): 807-816 (1983); Captopril Multicenter Research Group, J.A.C.C., 2(4): 755-763 (1983); The CONSENSUS Trial Study Group, N. Engl. J. Med., 316(23): 1429-1435 (1987); The SOLVD Investigators, N. Engl. J. Med., 325(5): 293-302 (1991). Further, they are useful in treating hypertension, left ventricular dysfunction, atherosclerotic vascular disease, and diabetic nephropathy. Brown and Vaughan, *supra*. However, despite proven efficacy, response to ACE inhibitors has been limited. For example, while prolonging survival in the setting of heart failure, ACE inhibitors appear to slow the progression towards end-stage heart failure, and substantial numbers of patients on ACE inhibitors have functional class III heart failure.

Moreover, improvement of functional capacity and exercise time is only small and mortality, although reduced, continues to be high. The CONSENSUS Trial Study Group, N. Engl. J. Med., 316(23): 1429-1435 (1987); The SOLVD Investigators, N. Engl. J. Med., 325(5): 293-302 (1991); Cohn *et al.*, N. Engl. J. Med., 325(5): 303-310 (1991); The Captopril-Digoxin Multicenter Research Group, JAMA, 259(4): 539-544 (1988). Hence, ACE inhibitors consistently appear unable to relieve symptoms in more than 60% of heart failure patients and reduce mortality of heart failure only by approximately 15-20%. For further adverse effects, see Brown and Vaughan,

*supra*.

An alternative to ACE inhibitors is represented by specific AT1 receptor antagonists. Clinical studies are planned to compare the efficacy of these two modalities in the treatment of cardiovascular and renal disease. However, animal model data suggests that the ACE/Ang II pathway, while clearly involved in cardiac hypertrophy, is not the only, or even the primary pathway active in this role. Mouse genetic "knockout" models have been made to test individual components of the pathway. In one such model, the primary cardiac receptor for Ang II, AT sub 1A, has been genetically deleted; these mice do not develop hypertrophy when Ang II is given experimentally (confirming the basic success of the model in eliminating hypertrophy secondary to Ang II). However, when the aorta is constricted in these animals (a model of hypertensive cardiac stress), the hearts still become hypertrophic. This suggests that alternative signaling pathways, not depending on this receptor (AT sub 1A), are activated in hypertension. ACE inhibitors would presumably not be able to inhibit these pathways. See, Harada *et al.*, Circulation, 97: 1952-1959 (1998). See also, Homcy, Circulation, 97: 1890-1892 (1998) regarding the enigma associated with the process and mechanism of cardiac hypertrophy.

About 750,000 patients suffer from acute myocardial infarction (AMI) annually, and approximately one-fourth of all deaths in the United States are due to AMI. In recent years, thrombolytic agents, *e.g.*, streptokinase, urokinase, and in particular tissue plasminogen activator (t-PA) have significantly increased the survival of patients who suffered myocardial infarction. When administered as a continuous intravenous infusion over 1.5 to 4 hours, t-PA produces coronary patency at 90 minutes in 69% to 90% of the treated patients. Topol *et al.*, Am. J. Cardiol., 61: 723-728 (1988); Neuhaus *et al.*, J. Am. Coll. Cardiol., 12: 581-587 (1988); Neuhaus *et al.*, J. Am. Coll. Cardiol., 14: 1566-1569 (1989). The highest patency rates have been reported with high dose or accelerated dosing regimens. Topol, J. Am. Coll. Cardiol., 15: 922-924 (1990). t-PA may also be administered as a single bolus, although due to its relatively short half-life, it is better suited for infusion therapy. Tebbe *et al.*, Am. J. Cardiol., 64: 448-453 (1989). A t-PA variant, specifically designed to have longer half-life and very high fibrin specificity, TNK t-PA (a T103N, N117Q, KHRR(296-299)AAAA t-PA variant, Keyt *et al.*, Proc. Natl. Acad. Sci. USA, 91: 3670-3674 (1994)) is particularly suitable for bolus administration. However, despite all these advances, the long-term prognosis of patient survival depends greatly on the post-infarction monitoring and treatment of the patients, which should include monitoring and treatment of cardiac hypertrophy.

### 2.3. Growth Factors

Various naturally occurring polypeptides reportedly induce the proliferation of endothelial cells. Among those polypeptides are the basic and acidic fibroblast growth factors (FGF) (Burgess and Maciag, Annual Rev. Biochem., 58: 575 (1989)), platelet-derived endothelial cell growth factor (PD-ECGF) (Ishikawa *et al.*, Nature, 338: 557 (1989)), and vascular endothelial growth factor (VEGF). Leung *et al.*, Science, 246: 1306 (1989); Ferrara and Henzel, Biochem. Biophys. Res. Commun., 161: 851 (1989); Tischer *et al.*, Biochem. Biophys. Res. Commun., 165: 1198 (1989); EP 471,754B granted July 31, 1996.

Media conditioned by cells transfected with the human VEGF (hVEGF) cDNA promoted the proliferation of capillary endothelial cells, whereas control cells did not. Leung *et al.*, Science, 246: 1306 (1989). Several

additional cDNAs were identified in human cDNA libraries that encode 121-, 189-, and 206-amino acid isoforms of hVEGF (also collectively referred to as hVEGF-related proteins). The 121-amino acid protein differs from hVEGF by virtue of the deletion of the 44 amino acids between residues 116 and 159 in hVEGF. The 189-amino acid protein differs from hVEGF by virtue of the insertion of 24 amino acids at residue 116 in hVEGF, and apparently is identical to human vascular permeability factor (hVPF). The 206-amino acid protein differs from hVEGF by virtue of an insertion of 41 amino acids at residue 116 in hVEGF. Houck *et al.*, Mol. Endocrin., **5**: 1806 (1991); Ferrara *et al.*, J. Cell. Biochem., **47**: 211 (1991); Ferrara *et al.*, Endocrine Reviews, **13**: 18 (1992); Keck *et al.*, Science, **246**: 1309 (1989); Connolly *et al.*, J. Biol. Chem., **264**: 20017 (1989); EP 370,989 published May 30, 1990.

It is now well established that angiogenesis, which involves the formation of new blood vessels from preexisting endothelium, is implicated in the pathogenesis of a variety of disorders. These include solid tumors and metastasis, atherosclerosis, retrolental fibroplasia, hemangiomas, chronic inflammation, intraocular neovascular syndromes such as proliferative retinopathies, *e.g.*, diabetic retinopathy, age-related macular degeneration (AMD), neovascular glaucoma, immune rejection of transplanted corneal tissue and other tissues, rheumatoid arthritis, and psoriasis. Folkman *et al.*, J. Biol. Chem., **267**: 10931-10934 (1992); Klagsbrun *et al.*, Annu. Rev. Physiol., **53**: 217-239 (1991); and Garner A., "Vascular diseases", In: Pathobiology of Ocular Disease. A Dynamic Approach, Garner A., Klintworth GK, eds., 2nd Edition (Marcel Dekker, NY, 1994), pp 1625-1710.

In the case of tumor growth, angiogenesis appears to be crucial for the transition from hyperplasia to neoplasia, and for providing nourishment for the growth and metastasis of the tumor. Folkman *et al.*, Nature, **339**: 58 (1989). The neovascularization allows the tumor cells to acquire a growth advantage and proliferative autonomy compared to the normal cells. A tumor usually begins as a single aberrant cell which can proliferate only to a size of a few cubic millimeters due to the distance from available capillary beds, and it can stay 'dormant' without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels not only allow for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells. Accordingly, a correlation has been observed between density of microvessels in tumor sections and patient survival in breast cancer as well as in several other tumors. Weidner *et al.*, N. Engl. J. Med., **324**: 1-6 (1991); Horak *et al.*, Lancet, **340**: 1120-1124 (1992); Macchiarini *et al.*, Lancet, **340**: 145-146 (1992). The precise mechanisms that control the angiogenic switch is not well understood, but it is believed that neovascularization of tumor mass results from the net balance of a multitude of angiogenesis stimulators and inhibitors (Folkman, 1995, Nat Med **1**(1):27-31).

The search for positive regulators of angiogenesis has yielded many candidates, including aFGF, bFGF, TGF- $\alpha$ , TGF- $\beta$ , HGF, TNF- $\alpha$ , angiogenin, IL-8, etc. Folkman *et al.*, J.B.C., *supra*, and Klagsbrun *et al.*, *supra*. The negative regulators so far identified include thrombospondin (Good *et al.*, Proc. Natl. Acad. Sci. USA, **87**: 6624-6628 (1990)), the 16-kilodalton N-terminal fragment of prolactin (Clapp *et al.*, Endocrinology, **133**: 1292-1299 (1993)), angiostatin (O'Reilly *et al.*, Cell, **79**: 315-328 (1994)), and endostatin. O'Reilly *et al.*, Cell, **88**: 277-285 (1996).

Work done over the last several years has established the key role of VEGF, not only in stimulating vascular endothelial cell proliferation, but also in inducing vascular permeability and angiogenesis. Ferrara *et al.*, Endocr. Rev., **18**: 4-25 (1997). The finding that the loss of even a single VEGF allele results in embryonic lethality points to an irreplaceable role played by this factor in the development and differentiation of the vascular system. Furthermore, VEGF has been shown to be a key mediator of neovascularization associated with tumors and intraocular disorders. Ferrara *et al.*, Endocr. Rev., *supra*. The VEGF mRNA is overexpressed by the majority of human tumors examined. Berkman *et al.*, J. Clin. Invest., **91**: 153-159 (1993); Brown *et al.*, Human Pathol., **26**: 86-91 (1995); Brown *et al.*, Cancer Res., **53**: 4727-4735 (1993); Mattern *et al.*, Brit. J. Cancer, **73**: 931-934 (1996); Dvorak *et al.*, Am. J. Pathol., **146**: 1029-1039 (1995).

Also, the concentration levels of VEGF in eye fluids are highly correlated to the presence of active proliferation of blood vessels in patients with diabetic and other ischemia-related retinopathies. Aiello *et al.*, N. Engl. J. Med., **331**: 1480-1487 (1994). Furthermore, recent studies have demonstrated the localization of VEGF in choroidal neovascular membranes in patients affected by AMD. Lopez *et al.*, Invest. Ophthalmol. Vis. Sci., **37**: 855-868 (1996).

Anti-VEGF neutralizing antibodies suppress the growth of a variety of human tumor cell lines in nude mice (Kim *et al.*, Nature, **362**: 841-844 (1993); Warren *et al.*, J. Clin. Invest., **95**: 1789-1797 (1995); Borgström *et al.*, Cancer Res., **56**: 4032-4039 (1996); Melnyk *et al.*, Cancer Res., **56**: 921-924 (1996)) and also inhibit intraocular angiogenesis in models of ischemic retinal disorders. Adamis *et al.*, Arch. Ophthalmol., **114**: 66-71 (1996). Therefore, anti-VEGF monoclonal antibodies or other inhibitors of VEGF action are promising candidates for the treatment of solid tumors and various intraocular neovascular disorders. Such antibodies are described, for example, in EP 817,648 published January 14, 1998 and in WO98/45331 and WO98/45332 both published October 15, 1998.

There exist several other growth factors and mitogens, including transforming oncogenes, that are capable of rapidly inducing a complex set of genes to be expressed by certain cells. Lau and Nathans, Molecular Aspects of Cellular Regulation, **6**: 165-202 (1991). These genes, which have been named immediate-early- or early-response genes, are transcriptionally activated within minutes after contact with a growth factor or mitogen, independent of *de novo* protein synthesis. A group of these intermediate-early genes encodes secreted, extracellular proteins that are needed for coordination of complex biological processes such as differentiation and proliferation, regeneration, and wound healing. Ryseck *et al.*, Cell Growth Differ., **2**: 235-233 (1991).

Highly-related proteins that belong to this group include *cef10* (Simmons *et al.*, Proc. Natl. Acad. Sci. USA, **86**: 1178-1182 (1989)), *cyr61*, which is rapidly activated by serum- or platelet-derived growth factor (PDGF) (O'Brien *et al.*, Mol. Cell Biol., **10**: 3569-3577 (1990)), human connective tissue growth factor (CTGF) (Bradham *et al.*, J. Cell. Biol., **114**: 1285-1294 (1991)), which is secreted by human vascular endothelial cells in high levels after activation with transforming growth factor beta (TGF- $\beta$ ), exhibits PDGF-like biological and immunological activities, and competes with PDGF for a particular cell surface receptor, *fisp-12* (Ryseck *et al.*, Cell Growth Differ., **2**: 235-233 (1991)), human vascular IBP-like growth factor (VIGF) (WO 96/17931), and *nov*, normally arrested in adult kidney cells, which was found to be overexpressed in myeloblastosis-associated-virus-type-1-induced nephroblastomas. Joliet *et al.*, Mol. Cell. Biol., **12**: 10-21 (1992).

The expression of these immediate-early genes acts as "third messengers" in the cascade of events triggered by growth factors. It is also thought that they are needed to integrate and coordinate complex biological processes, such as differentiation and wound healing in which cell proliferation is a common event.

As additional mitogens, insulin-like growth factor binding proteins (IGFBPs) have been shown, in complex with insulin-like growth factor (IGF), to stimulate increased binding of IGF to fibroblast and smooth muscle cell surface receptors. Clemmons *et al.*, *J. Clin. Invest.*, **77**: 1548 (1986). Inhibitory effects of IGFBP on various IGF actions *in vitro* include stimulation of glucose transport by adipocytes, sulfate incorporation by chondrocytes, and thymidine incorporation in fibroblast. Zapf *et al.*, *J. Clin. Invest.*, **63**: 1077 (1979). In addition, inhibitory effects of IGFBPs on growth factor-mediated mitogen activity in normal cells have been shown.

#### 2.4. Need for Further Treatments

In view of the role of vascular endothelial cell growth and angiogenesis in many diseases and disorders, it is desirable to have a means of reducing or inhibiting one or more of the biological effects causing these processes. It is also desirable to have a means of assaying for the presence of pathogenic polypeptides in normal and diseased conditions, and especially cancer. Further, in a specific aspect, as there is no generally applicable therapy for the treatment of cardiac hypertrophy, the identification of factors that can prevent or reduce cardiac myocyte hypertrophy is of primary importance in the development of new therapeutic strategies to inhibit pathophysiological cardiac growth. While there are several treatment modalities for various cardiovascular and oncologic disorders, there is still a need for additional therapeutic approaches.

### 3. Summary of the Invention

The present invention provides compositions and methods for modulating (*e.g.*, promoting or inhibiting) angiogenesis and/or cardiovascularization in mammals. The present invention is based on the identification of compounds (*i.e.*, proteins) that test positive in various cardiovascular assays that test modulation (*e.g.*, promotion or inhibition) of certain biological activities. Accordingly, the compounds are believed to be useful drugs and/or drug components for the diagnosis and/or treatment (including prevention and amelioration) of disorders where such effects are desired, such as the promotion or inhibition of angiogenesis, inhibition or stimulation of vascular endothelial cell growth, stimulation of growth or proliferation of vascular endothelial cells, inhibition of tumor growth, inhibition of angiogenesis-dependent tissue growth, stimulation of angiogenesis-dependent tissue growth, inhibition of cardiac hypertrophy and stimulation of cardiac hypertrophy, *e.g.*, for the treatment of congestive heart failure. In addition, the compositions and methods of the invention provide for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of angiogenesis-related disorders, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such angiogenic-related disorders.

In one embodiment, the present invention provides a composition comprising a PRO polypeptide, an agonist or antagonist thereof, or an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide, agonist, antagonist

or antibody. In another aspect, the composition comprises a further active ingredient, namely, a cardiovascular, endothelial or angiogenic agent or an angiostatic agent, preferably an angiogenic or angiostatic agent. Preferably, the composition is sterile. The PRO polypeptide, agonist, antagonist or antibody may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Preserved liquid pharmaceutical formulations might contain multiple doses of PRO polypeptide, agonist, antagonist or antibody, and might, therefore, be suitable for repeated use. In a preferred embodiment, where the composition comprises an antibody, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

In a further embodiment, the present invention provides a method for preparing such a composition useful for the treatment of a cardiovascular, endothelial or angiogenic disorder comprising admixing a therapeutically effective amount of a PRO polypeptide, agonist, antagonist or antibody with a pharmaceutically acceptable carrier.

In a still further aspect, the present invention provides an article of manufacture comprising:

- (a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;
- (b) a container containing said composition; and
- (c) a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of a cardiovascular, endothelial or angiogenic disorder, wherein the agonist or antagonist may be an antibody which binds to the PRO polypeptide. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

- (a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and
- (b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

- (a) contacting cells and a test compound to be screened under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and
- (b) measuring the proliferation of said cells to determine if the test compound is an effective agonist, wherein the stimulation of cell proliferation is indicative of said test compound being an effective agonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the activity of a PRO polypeptide comprising contacting a test compound with a PRO polypeptide under conditions and for a time sufficient to allow the test compound and polypeptide to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific preferred aspect, either the test compound or the PRO polypeptide is immobilized on a solid support. In another preferred aspect, the non-immobilized component carries a detectable

label. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

5 (b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another preferred aspect, this process comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and

(b) measuring the proliferation of the cells to determine if the test compound is an effective antagonist.

10 In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally expresses the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

15 (a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

In a still further embodiment, the invention provides a compound that inhibits the expression of a PRO polypeptide, such as a compound that is identified by the methods set forth above.

20 Another aspect of the present invention is directed to an agonist or an antagonist of a PRO polypeptide which may optionally be identified by the methods described above.

One type of antagonist of a PRO polypeptide that inhibits one or more of the functions or activities of the PRO polypeptide is an antibody. Hence, in another aspect, the invention provides an isolated antibody that binds a PRO polypeptide. In a preferred aspect, the antibody is a monoclonal antibody, which preferably has non-human complementarity-determining-region (CDR) residues and human framework-region (FR) residues. The antibody  
25 may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a single-chain antibody, or a humanized antibody. Preferably, the antibody specifically binds to the polypeptide.

In a still further aspect, the present invention provides a method for diagnosing a disease or susceptibility to a disease which is related to a mutation in a PRO polypeptide-encoding nucleic acid sequence comprising  
30 determining the presence or absence of said mutation in the PRO polypeptide nucleic acid sequence, wherein the presence or absence of said mutation is indicative of the presence of said disease or susceptibility to said disease.

In a still further aspect, the invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal which comprises analyzing the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from said mammal, and (b) in a control sample of known  
35 normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in said mammal. The expression of a gene encoding a PRO polypeptide may optionally be accomplished by measuring



the level of mRNA or the polypeptide in the test sample as compared to the control sample.

In a still further aspect, the present invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of said PRO polypeptide in said test sample is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in said mammal.

In a still further embodiment, the invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and the PRO polypeptide in the test sample, wherein the formation of said complex is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in the mammal. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger or smaller quantity of complexes formed in the test sample indicates the presence of a cardiovascular, endothelial or angiogenic dysfunction in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected to have a cardiovascular, endothelial or angiogenic disorder.

In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a sample suspected of containing the PRO polypeptide to an anti-PRO antibody and determining binding of said antibody to a component of said sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

In further aspects, the invention provides a cardiovascular, endothelial or angiogenic disorder diagnostic kit comprising an anti-PRO antibody and a carrier in suitable packaging. Preferably, such kit further comprises instructions for using said antibody to detect the presence of the PRO polypeptide. Preferably, the carrier is a buffer, for example. Preferably, the cardiovascular, endothelial or angiogenic disorder is cancer.

In yet another embodiment, the present invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide. Preferably, the disorder is cardiac hypertrophy, trauma such as wounds or burns, or a type of cancer. In a further aspect, the mammal is further exposed to angioplasty or a drug that treats cardiovascular, endothelial or angiogenic disorders such as ACE inhibitors or chemotherapeutic agents if the cardiovascular, endothelial or angiogenic disorder is a type of cancer. Preferably, the mammal is human, preferably one who is at risk of developing cardiac hypertrophy and more preferably has suffered myocardial infarction.

In another preferred aspect, the cardiac hypertrophy is characterized by the presence of an elevated level of  $\text{PGF}_{2\alpha}$ . Alternatively, the cardiac hypertrophy may be induced by myocardial infarction, wherein preferably the administration of the PRO polypeptide is initiated within 48 hours, more preferably within 24 hours, following myocardial infarction.

In another preferred embodiment, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy and said PRO polypeptide is administered together with a cardiovascular, endothelial or angiogenic agent. The preferred cardiovascular, endothelial or angiogenic agent for this purpose is selected from the group consisting of an antihypertensive drug, an ACE inhibitor, an endothelin receptor antagonist and a thrombolytic agent. If a thrombolytic agent is administered, preferably the PRO polypeptide is administered following administration of such agent. More preferably, the thrombolytic agent is recombinant human tissue plasminogen activator.

In another preferred aspect, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy and the PRO polypeptide is administered following primary angioplasty for the treatment of acute myocardial infarction, preferably wherein the mammal is further exposed to angioplasty or a cardiovascular, endothelial, or angiogenic agent.

In another preferred embodiment, the cardiovascular, endothelial or angiogenic disorder is a cancer and the PRO polypeptide is administered in combination with a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent.

In a further embodiment, the invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide agonist, antagonist or anti-PRO antibody. Preferably, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy, trauma, a cancer, or age-related macular degeneration. Also preferred is where the mammal is human, and where an effective amount of an angiogenic or angiostatic agent is administered in conjunction with the agonist, antagonist or anti-PRO antibody.

In still further embodiments, the invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the gene is administered via *ex vivo* gene therapy. In a further preferred embodiment, the gene is comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral, or retroviral vector.

In yet another aspect, the invention provides a recombinant retroviral particle comprising a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the retroviral vector is in association with retroviral structural proteins. Preferably, the signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention supplies an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce

recombinant retroviral particles.

5 In yet another embodiment, the invention provides a method for inhibiting endothelial cell growth in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein endothelial cell growth in said mammal is inhibited, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human and the endothelial cell growth is associated with a tumor or a retinal disorder.

10 In yet another embodiment, the invention provides a method for stimulating endothelial cell growth in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein endothelial cell growth in said mammal is stimulated, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human.

15 In yet another embodiment, the invention provides a method for inhibiting cardiac hypertrophy in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein cardiac hypertrophy in said mammal is inhibited, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human and the cardiac hypertrophy has been induced by myocardial infarction.

20 In yet another embodiment, the invention provides a method for stimulating cardiac hypertrophy in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein cardiac hypertrophy in said mammal is stimulated, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human who suffers from congestive heart failure.

25 In yet another embodiment, the invention provides a method for inhibiting angiogenesis induced by a PRO polypeptide in a mammal comprising administering a therapeutically effective amount of an anti-PRO antibody to the mammal. Preferably, the mammal is a human, and more preferably the mammal has a tumor or a retinal disorder.

30 In yet another embodiment, the invention provides a method for stimulating angiogenesis induced by a PRO polypeptide in a mammal comprising administering a therapeutically effective amount of a PRO polypeptide to the mammal. Preferably, the mammal is a human, and more preferably angiogenesis would promote tissue regeneration or wound healing.

35 In yet another embodiment, the invention provides a method for modulating (*e.g.*, inhibiting or stimulating) endothelial cell growth in a mammal comprising administering to the mammal a PRO21, PRO181, PRO205, PRO214, PRO221, PRO229, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO365, PRO444, PRO533, PRO697, PRO720, PRO725, PRO771, PRO788, PRO791, PRO819, PRO827, PRO828, PRO836, PRO846, PRO865, PRO1005, PRO1006, PRO1007, PRO1025, PRO1029, PRO1054, PRO1071, PRO1075, PRO1079, PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1184, PRO1186, PRO1190, PRO1192, PRO1195, PRO1244, PRO1272, PRO1273, PRO1274, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1411, PRO1412, PRO1419, PRO1474, PRO1477, PRO1488, PRO1508, PRO1550,

PRO1556, PRO1760, PRO1782, PRO1787, PRO1801, PRO1868, PRO1887, PRO1890, PRO3438, PRO3444, PRO4302, PRO4324, PRO4333, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4405, PRO4408, PRO4422, PRO4425, PRO4499, PRO5723, PRO5725, PRO5737, PRO5776, PRO6006, PRO6029, PRO6071, PRO7436, PRO9771, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21055, PRO21384 or PRO28631 polypeptide, agonist or antagonist thereof, wherein endothelial cell growth in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inhibiting or stimulating) smooth muscle cell growth in a mammal comprising administering to the mammal a PRO162, PRO181, PRO182, PRO195, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1080, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1265, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1309, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1488, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4302, PRO4333, PRO4345, PRO4353, PRO4354, PRO4405, PRO4408, PRO4430, PRO4503, PRO5725, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 or PRO21366 polypeptide, agonist or antagonist thereof, wherein endothelial cell growth in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) cardiac hypertrophy in a mammal comprising administering to the mammal a PRO21 polypeptide, agonist or antagonist thereof, wherein cardiac hypertrophy in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) endothelial cell apoptosis in a mammal comprising administering to the mammal a PRO4302 polypeptide, agonist or antagonist thereof, wherein cardiac hypertrophy in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, stimulating or inhibiting) angiogenesis in a mammal comprising administering a therapeutically effective amount of a PRO1376 or PRO1449 polypeptide, agonist or antagonist thereof to the mammal, wherein said angiogenesis is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) angiogenesis by modulating (*e.g.*, inducing or reducing) endothelial cell tube formation in a mammal comprising administering to the mammal a PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873, PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 or PRO7261 polypeptide, agonist or antagonist thereof, wherein endothelial cell tube formation in said mammal is modulated.

In other embodiments of the present invention, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98%

nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect of the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 350, 400, 450, 500, 600, 700 or 800 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides an isolated PRO polypeptide encoded by any of the isolated

nucleic acid sequences hereinabove identified.

5 In a certain aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

10 In a further aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

15 In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and that is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

20 Another aspect of the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

25 In yet another embodiment, the invention provides agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

30 In a further embodiment, the invention provides a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention provides a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

35 Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In additional embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, yeast, or Baculovirus-infected insect cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In yet another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

#### 4. Brief Description of the Drawings

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO181 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA23330-1390".

Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence PRO178 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA23339-1130".

Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO444 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA26846-1397".

Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO195 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA26847-1395".

Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a native sequence PRO182 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA27865-1091".

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID

NO:9 shown in Figure 9.

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO205 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA30868-1156".

5 Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO204 cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA30871-1157".

Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

10 Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO1873 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA30880".

Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

15 Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO214 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA32286-1191".

Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO221 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA33089-1132".

20 Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO228 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA33092-1202".

25 Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO229 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA33100-1159".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

30 Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO230 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA33223-1136".

Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

35 Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO7223 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA34385".

Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.



Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO241 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA34392-1170".

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

5        Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a native sequence PRO263 cDNA, wherein SEQ ID NO:31 is a clone designated herein as "DNA34431-1177".

Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

10       Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a native sequence PRO321 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA34433-1308".

Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO231 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA34434-1139".

15       Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a native sequence PRO238 cDNA, wherein SEQ ID NO:37 is a clone designated herein as "DNA35600-1162".

20       Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a native sequence PRO247 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA35673-1201".

Figure 40 shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

25       Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a native sequence PRO256 cDNA, wherein SEQ ID NO:41 is a clone designated herein as "DNA35880-1160".

Figure 42 shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

30       Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a native sequence PRO258 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA35918-1174".

Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a native sequence PRO265 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA36350-1158".

35       Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO21 cDNA, wherein SEQ

ID NO:47 is a clone designated herein as "DNA36638-1056".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

5 Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO295 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA38268-1188".

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO302 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA40370-1217".

10 Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO301 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA40628-1216".

15 Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO337 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA43316-1237".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ ID NO:55 shown in Figure 55.

20 Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO7248 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA44195".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

25 Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO846 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA44196-1353".

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO1864 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA45409-2511".

30 Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO363 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA45419-1252".

35 Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO730 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA45624-1400".

Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO365 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA46777-1253".

5        Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO532 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA48335".

10       Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO322 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA48336-1309".

Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

15       Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO1120 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA48606-1479".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

20       Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence PRO7261 cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA49149".

Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO533 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA49435-1219".

25       Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence PRO724 cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA49631-1328".

30       Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) of a native sequence PRO734 cDNA, wherein SEQ ID NO:81 is a clone designated herein as "DNA49817".

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:81 shown in Figure 81.

35       Figure 83 shows a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO771 cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA49829-1346".

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID

NO:83 shown in Figure 83.

Figure 85 shows a nucleotide sequence (SEQ ID NO:85) of a native sequence PRO2010 cDNA, wherein SEQ ID NO:85 is a clone designated herein as "DNA50792".

5 Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO871 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA50919-1361".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

10 Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO697 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "DNA50920-1325".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

15 Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO1083 cDNA, wherein SEQ ID NO:91 is a clone designated herein as "DNA50921-1458".

Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO725 cDNA, wherein SEQ ID NO:93 is a clone designated herein as "DNA52758-1399".

20 Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO720 cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA53517-1366-1".

25 Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO738 cDNA, wherein SEQ ID NO:97 is a clone designated herein as "DNA53915-1258".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

30 Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO865 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA53974-1401".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

35 Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO840 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA53987-1438".

Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO1080 cDNA, wherein SEQ ID NO:103 is a clone designated herein as "DNA56047-1456".

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

5        Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO1079 cDNA, wherein SEQ ID NO:105 is a clone designated herein as "DNA56050-1455".

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

10        Figure 107 shows a nucleotide sequence (SEQ ID NO:107) of a native sequence PRO793 cDNA, wherein SEQ ID NO:107 is a clone designated herein as "DNA56110-1437".

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) of a native sequence PRO788 cDNA, wherein SEQ ID NO:109 is a clone designated herein as "DNA56405-1357".

15        Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:109 shown in Figure 109.

Figure 111 shows a nucleotide sequence (SEQ ID NO:111) of a native sequence PRO938 cDNA, wherein SEQ ID NO:111 is a clone designated herein as "DNA56433-1406".

20        Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO1012 cDNA, wherein SEQ ID NO:113 is a clone designated herein as "DNA56439-1376".

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

25        Figure 115 shows a nucleotide sequence (SEQ ID NO:115) of a native sequence PRO1477 cDNA, wherein SEQ ID NO:115 is a clone designated herein as "DNA56529-1647".

Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:115 shown in Figure 115.

30        Figure 117 shows a nucleotide sequence (SEQ ID NO:117) of a native sequence PRO1134 cDNA, wherein SEQ ID NO:117 is a clone designated herein as "DNA56865-1491".

Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) of a native sequence PRO162 cDNA, wherein SEQ ID NO:119 is a clone designated herein as "DNA56965-1356".

35        Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) of a native sequence PRO1114 cDNA, wherein

SEQ ID NO:121 is a clone designated herein as "DNA57033-1403-1".

Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

5 Figure 123 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO828 cDNA, wherein SEQ ID NO:123 is a clone designated herein as "DNA57037-1444".

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO827 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA57039-1402".

10 Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO1075 cDNA, wherein SEQ ID NO:127 is a clone designated herein as "DNA57689-1385".

15 Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO1007 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA57690-1374".

Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

20 Figure 131 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO826 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA57694-1341".

Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

25 Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO819 cDNA, wherein SEQ ID NO:132 is a clone designated herein as "DNA57695-1340".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:133 shown in Figure 133.

Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO1006 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA57699-1412".

30 Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO982 cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA57700-1408".

35 Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO1005 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA57708-1411".

Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO791 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA57838-1337".

5        Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) of a native sequence PRO1071 cDNA, wherein SEQ ID NO:143 is a clone designated herein as "DNA58847-1383".

10       Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:143 shown in Figure 43.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) of a native sequence PRO1415 cDNA, wherein SEQ ID NO:145 is a clone designated herein as "DNA58852-1637".

Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 145.

15       Figure 147 shows a nucleotide sequence (SEQ ID NO:147) of a native sequence PRO1054 cDNA, wherein SEQ ID NO:147 is a clone designated herein as "DNA58853-1423".

Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 147.

20       Figure 149 shows a nucleotide sequence (SEQ ID NO:149) of a native sequence PRO1411 cDNA, wherein SEQ ID NO:149 is a clone designated herein as "DNA59212-1627".

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 149.

Figure 151 shows a nucleotide sequence (SEQ ID NO:151) of a native sequence PRO1184 cDNA, wherein SEQ ID NO:151 is a clone designated herein as "DNA59220-1514".

25       Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:151 shown in Figure 151.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) of a native sequence PRO1029 cDNA, wherein SEQ ID NO:153 is a clone designated herein as "DNA59493-1420".

30       Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) of a native sequence PRO1139 cDNA, wherein SEQ ID NO:155 is a clone designated herein as "DNA59497-1496".

Figure 156 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 155.

35       Figure 157 shows a nucleotide sequence (SEQ ID NO:157) of a native sequence PRO1190 cDNA, wherein SEQ ID NO:157 is a clone designated herein as "DNA59586-1520".

Figure 158 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ

ID NO:157 shown in Figure 157.

Figure 159 shows a nucleotide sequence (SEQ ID NO:159) of a native sequence PRO1309 cDNA, wherein SEQ ID NO:159 is a clone designated herein as "DNA59588-1571".

5 Figure 160 shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of SEQ ID NO:159 shown in Figure 159.

Figure 161 shows a nucleotide sequence (SEQ ID NO:161) of a native sequence PRO836 cDNA, wherein SEQ ID NO:161 is a clone designated herein as "DNA59620-1463".

Figure 162 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 161.

10 Figure 163 shows a nucleotide sequence (SEQ ID NO:163) of a native sequence PRO1025 cDNA, wherein SEQ ID NO:163 is a clone designated herein as "DNA59622-1334".

Figure 164 shows the amino acid sequence (SEQ ID NO:164) derived from the coding sequence of SEQ ID NO:163 shown in Figure 163.

15 Figure 165 shows a nucleotide sequence (SEQ ID NO:165) of a native sequence PRO1131 cDNA, wherein SEQ ID NO:165 is a clone designated herein as "DNA59777-1480".

Figure 166 shows the amino acid sequence (SEQ ID NO:166) derived from the coding sequence of SEQ ID NO:165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) of a native sequence PRO1182 cDNA, wherein SEQ ID NO:167 is a clone designated herein as "DNA59848-1512".

20 Figure 168 shows the amino acid sequence (SEQ ID NO:168) derived from the coding sequence of SEQ ID NO:167 shown in Figure 167.

Figure 169 shows a nucleotide sequence (SEQ ID NO:169) of a native sequence PRO1155 cDNA, wherein SEQ ID NO:169 is a clone designated herein as "DNA59849-1504".

25 Figure 170 shows the amino acid sequence (SEQ ID NO:170) derived from the coding sequence of SEQ ID NO:169 shown in Figure 169.

Figure 171 shows a nucleotide sequence (SEQ ID NO:171) of a native sequence PRO1186 cDNA, wherein SEQ ID NO:171 is a clone designated herein as "DNA60621-1516".

Figure 172 shows the amino acid sequence (SEQ ID NO:172) derived from the coding sequence of SEQ ID NO:171 shown in Figure 171.

30 Figure 173 shows a nucleotide sequence (SEQ ID NO:173) of a native sequence PRO1198 cDNA, wherein SEQ ID NO:173 is a clone designated herein as "DNA60622-1525".

Figure 174 shows the amino acid sequence (SEQ ID NO:174) derived from the coding sequence of SEQ ID NO:173 shown in Figure 173.

35 Figure 175 shows a nucleotide sequence (SEQ ID NO:175) of a native sequence PRO1265 cDNA, wherein SEQ ID NO:175 is a clone designated herein as "DNA60764-1533".

Figure 176 shows the amino acid sequence (SEQ ID NO:176) derived from the coding sequence of SEQ ID NO:175 shown in Figure 175.



Figure 177 shows a nucleotide sequence (SEQ ID NO:177) of a native sequence PRO1361 cDNA, wherein SEQ ID NO:177 is a clone designated herein as "DNA60783-1611".

Figure 178 shows the amino acid sequence (SEQ ID NO:178) derived from the coding sequence of SEQ ID NO:177 shown in Figure 177.

5        Figure 179 shows a nucleotide sequence (SEQ ID NO:179) of a native sequence PRO1287 cDNA, wherein SEQ ID NO:179 is a clone designated herein as "DNA61755-1554".

Figure 180 shows the amino acid sequence (SEQ ID NO:180) derived from the coding sequence of SEQ ID NO:179 shown in Figure 179.

10       Figure 181 shows a nucleotide sequence (SEQ ID NO:181) of a native sequence PRO1308 cDNA, wherein SEQ ID NO:181 is a clone designated herein as "DNA62306-1570".

Figure 182 shows the amino acid sequence (SEQ ID NO:182) derived from the coding sequence of SEQ ID NO:181 shown in Figure 181.

Figure 183 shows a nucleotide sequence (SEQ ID NO:183) of a native sequence PRO4313 cDNA, wherein SEQ ID NO:183 is a clone designated herein as "DNA62312-2558".

15       Figure 184 shows the amino acid sequence (SEQ ID NO:184) derived from the coding sequence of SEQ ID NO:183 shown in Figure 183.

Figure 185 shows a nucleotide sequence (SEQ ID NO:185) of a native sequence PRO1192 cDNA, wherein SEQ ID NO:185 is a clone designated herein as "DNA62814-1521".

20       Figure 186 shows the amino acid sequence (SEQ ID NO:186) derived from the coding sequence of SEQ ID NO:185 shown in Figure 185.

Figure 187 shows a nucleotide sequence (SEQ ID NO:187) of a native sequence PRO1160 cDNA, wherein SEQ ID NO:187 is a clone designated herein as "DNA62872-1509".

Figure 188 shows the amino acid sequence (SEQ ID NO:188) derived from the coding sequence of SEQ ID NO:187 shown in Figure 187.

25       Figure 189 shows a nucleotide sequence (SEQ ID NO:189) of a native sequence PRO1244 cDNA, wherein SEQ ID NO:189 is a clone designated herein as "DNA64883-1526".

Figure 190 shows the amino acid sequence (SEQ ID NO:190) derived from the coding sequence of SEQ ID NO:189 shown in Figure 189.

30       Figure 191 shows a nucleotide sequence (SEQ ID NO:191) of a native sequence PRO1356 cDNA, wherein SEQ ID NO:191 is a clone designated herein as "DNA64886-1601".

Figure 192 shows the amino acid sequence (SEQ ID NO:192) derived from the coding sequence of SEQ ID NO:191 shown in Figure 191.

Figure 193 shows a nucleotide sequence (SEQ ID NO:193) of a native sequence PRO1274 cDNA, wherein SEQ ID NO:193 is a clone designated herein as "DNA64889-1541".

35       Figure 194 shows the amino acid sequence (SEQ ID NO:194) derived from the coding sequence of SEQ ID NO:193 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO:195) of a native sequence PRO1272 cDNA, wherein

SEQ ID NO:195 is a clone designated herein as "DNA64896-1539".

Figure 196 shows the amino acid sequence (SEQ ID NO:196) derived from the coding sequence of SEQ ID NO:195 shown in Figure 195.

5 Figure 197 shows a nucleotide sequence (SEQ ID NO:197) of a native sequence PRO1412 cDNA, wherein SEQ ID NO:197 is a clone designated herein as "DNA64897-1628".

Figure 198 shows the amino acid sequence (SEQ ID NO:198) derived from the coding sequence of SEQ ID NO:197 shown in Figure 197.

Figure 199 shows a nucleotide sequence (SEQ ID NO:199) of a native sequence PRO1286 cDNA, wherein SEQ ID NO:199 is a clone designated herein as "DNA64903-1553".

10 Figure 200 shows the amino acid sequence (SEQ ID NO:200) derived from the coding sequence of SEQ ID NO:199 shown in Figure 199.

Figure 201 shows a nucleotide sequence (SEQ ID NO:201) of a native sequence PRO1347 cDNA, wherein SEQ ID NO:201 is a clone designated herein as "DNA64950-1590".

15 Figure 202 shows the amino acid sequence (SEQ ID NO:202) derived from the coding sequence of SEQ ID NO:201 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO:203) of a native sequence PRO1273 cDNA, wherein SEQ ID NO:203 is a clone designated herein as "DNA65402-1540".

Figure 204 shows the amino acid sequence (SEQ ID NO:204) derived from the coding sequence of SEQ ID NO:203 shown in Figure 203.

20 Figure 205 shows a nucleotide sequence (SEQ ID NO:205) of a native sequence PRO1283 cDNA, wherein SEQ ID NO:205 is a clone designated herein as "DNA65404-1551".

Figure 206 shows the amino acid sequence (SEQ ID NO:206) derived from the coding sequence of SEQ ID NO:205 shown in Figure 205.

25 Figure 207 shows a nucleotide sequence (SEQ ID NO:207) of a native sequence PRO1279 cDNA, wherein SEQ ID NO:207 is a clone designated herein as "DNA65405-1547".

Figure 208 shows the amino acid sequence (SEQ ID NO:208) derived from the coding sequence of SEQ ID NO:207 shown in Figure 207.

Figure 209 shows a nucleotide sequence (SEQ ID NO:209) of a native sequence PRO1306 cDNA, wherein SEQ ID NO:209 is a clone designated herein as "DNA65410-1569".

30 Figure 210 shows the amino acid sequence (SEQ ID NO:210) derived from the coding sequence of SEQ ID NO:209 shown in Figure 209.

Figure 211 shows a nucleotide sequence (SEQ ID NO:211) of a native sequence PRO1195 cDNA, wherein SEQ ID NO:211 is a clone designated herein as "DNA65412-1523".

35 Figure 212 shows the amino acid sequence (SEQ ID NO:212) derived from the coding sequence of SEQ ID NO:211 shown in Figure 211.

Figure 213 shows a nucleotide sequence (SEQ ID NO:213) of a native sequence PRO4995 cDNA, wherein SEQ ID NO:213 is a clone designated herein as "DNA66307-2661".

Figure 214 shows the amino acid sequence (SEQ ID NO:214) derived from the coding sequence of SEQ ID NO:213 shown in Figure 213.

Figure 215 shows a nucleotide sequence (SEQ ID NO:215) of a native sequence PRO1382 cDNA, wherein SEQ ID NO:215 is a clone designated herein as "DNA66526-1616".

5        Figure 216 shows the amino acid sequence (SEQ ID NO:216) derived from the coding sequence of SEQ ID NO:215 shown in Figure 215.

Figure 217 shows a nucleotide sequence (SEQ ID NO:217) of a native sequence PRO1325 cDNA, wherein SEQ ID NO:217 is a clone designated herein as "DNA66659-1593".

10       Figure 218 shows the amino acid sequence (SEQ ID NO:218) derived from the coding sequence of SEQ ID NO:217 shown in Figure 217.

Figure 219 shows a nucleotide sequence (SEQ ID NO:219) of a native sequence PRO1329 cDNA, wherein SEQ ID NO:219 is a clone designated herein as "DNA66660-1585".

Figure 220 shows the amino acid sequence (SEQ ID NO:220) derived from the coding sequence of SEQ ID NO:219 shown in Figure 219.

15       Figure 221 shows a nucleotide sequence (SEQ ID NO:221) of a native sequence PRO1338 cDNA, wherein SEQ ID NO:221 is a clone designated herein as "DNA66667-1596".

Figure 222 shows the amino acid sequence (SEQ ID NO:222) derived from the coding sequence of SEQ ID NO:221 shown in Figure 221.

20       Figure 223 shows a nucleotide sequence (SEQ ID NO:223) of a native sequence PRO1337 cDNA, wherein SEQ ID NO:223 is a clone designated herein as "DNA66672-1586".

Figure 224 shows the amino acid sequence (SEQ ID NO:224) derived from the coding sequence of SEQ ID NO:223 shown in Figure 223.

Figure 225 shows a nucleotide sequence (SEQ ID NO:225) of a native sequence PRO1343 cDNA, wherein SEQ ID NO:225 is a clone designated herein as "DNA66675-1587".

25       Figure 226 shows the amino acid sequence (SEQ ID NO:226) derived from the coding sequence of SEQ ID NO:225 shown in Figure 225.

Figure 227 shows a nucleotide sequence (SEQ ID NO:227) of a native sequence PRO1376 cDNA, wherein SEQ ID NO:227 is a clone designated herein as "DNA67300-1605".

30       Figure 228 shows the amino acid sequence (SEQ ID NO:228) derived from the coding sequence of SEQ ID NO:227 shown in Figure 227.

Figure 229 shows a nucleotide sequence (SEQ ID NO:229) of a native sequence PRO1434 cDNA, wherein SEQ ID NO:229 is a clone designated herein as "DNA68818-2536".

Figure 230 shows the amino acid sequence (SEQ ID NO:230) derived from the coding sequence of SEQ ID NO:229 shown in Figure 229.

35       Figure 231 shows a nucleotide sequence (SEQ ID NO:231) of a native sequence PRO3579 cDNA, wherein SEQ ID NO:231 is a clone designated herein as "DNA68862-2546".

Figure 232 shows the amino acid sequence (SEQ ID NO:232) derived from the coding sequence of SEQ

ID NO:231 shown in Figure 231.

Figure 233 shows a nucleotide sequence (SEQ ID NO:233) of a native sequence PRO1387 cDNA, wherein SEQ ID NO:233 is a clone designated herein as "DNA68872-1620".

5 Figure 234 shows the amino acid sequence (SEQ ID NO:234) derived from the coding sequence of SEQ ID NO:233 shown in Figure 233.

Figure 235 shows a nucleotide sequence (SEQ ID NO:235) of a native sequence PRO1419 cDNA, wherein SEQ ID NO:235 is a clone designated herein as "DNA71290-1630".

Figure 236 shows the amino acid sequence (SEQ ID NO:236) derived from the coding sequence of SEQ ID NO:235 shown in Figure 235.

10 Figure 237 shows a nucleotide sequence (SEQ ID NO:237) of a native sequence PRO1488 cDNA, wherein SEQ ID NO:237 is a clone designated herein as "DNA73736-1657".

Figure 238 shows the amino acid sequence (SEQ ID NO:238) derived from the coding sequence of SEQ ID NO:237 shown in Figure 237.

15 Figure 239 shows a nucleotide sequence (SEQ ID NO:239) of a native sequence PRO1474 cDNA, wherein SEQ ID NO:239 is a clone designated herein as "DNA73739-1645".

Figure 240 shows the amino acid sequence (SEQ ID NO:240) derived from the coding sequence of SEQ ID NO:239 shown in Figure 239.

Figure 241 shows a nucleotide sequence (SEQ ID NO:241) of a native sequence PRO1508 cDNA, wherein SEQ ID NO:241 is a clone designated herein as "DNA73742-1662".

20 Figure 242 shows the amino acid sequence (SEQ ID NO:242) derived from the coding sequence of SEQ ID NO:241 shown in Figure 241.

Figure 243 shows a nucleotide sequence (SEQ ID NO:243) of a native sequence PRO1754 cDNA, wherein SEQ ID NO:243 is a clone designated herein as "DNA76385-1692".

25 Figure 244 shows the amino acid sequence (SEQ ID NO:244) derived from the coding sequence of SEQ ID NO:243 shown in Figure 243.

Figure 245 shows a nucleotide sequence (SEQ ID NO:245) of a native sequence PRO1550 cDNA, wherein SEQ ID NO:245 is a clone designated herein as "DNA76393-1664".

Figure 246 shows the amino acid sequence (SEQ ID NO:246) derived from the coding sequence of SEQ ID NO:245 shown in Figure 245.

30 Figure 247 shows a nucleotide sequence (SEQ ID NO:247) of a native sequence PRO1758 cDNA, wherein SEQ ID NO:247 is a clone designated herein as "DNA76399-1700".

Figure 248 shows the amino acid sequence (SEQ ID NO:248) derived from the coding sequence of SEQ ID NO:247 shown in Figure 247.

35 Figure 249 shows a nucleotide sequence (SEQ ID NO:249) of a native sequence PRO1917 cDNA, wherein SEQ ID NO:249 is a clone designated herein as "DNA76400-2528".

Figure 250 shows the amino acid sequence (SEQ ID NO:250) derived from the coding sequence of SEQ ID NO:249 shown in Figure 249.

Figure 251 shows a nucleotide sequence (SEQ ID NO:251) of a native sequence PRO1787 cDNA, wherein SEQ ID NO:251 is a clone designated herein as "DNA76510-2504".

Figure 252 shows the amino acid sequence (SEQ ID NO:252) derived from the coding sequence of SEQ ID NO:251 shown in Figure 251.

5        Figure 253 shows a nucleotide sequence (SEQ ID NO:253) of a native sequence PRO1556 cDNA, wherein SEQ ID NO:253 is a clone designated herein as "DNA76529-1666".

Figure 254 shows the amino acid sequence (SEQ ID NO:254) derived from the coding sequence of SEQ ID NO:253 shown in Figure 253.

10       Figure 255 shows a nucleotide sequence (SEQ ID NO:255) of a native sequence PRO1760 cDNA, wherein SEQ ID NO:255 is a clone designated herein as "DNA76532-1702".

Figure 256 shows the amino acid sequence (SEQ ID NO:256) derived from the coding sequence of SEQ ID NO:255 shown in Figure 255.

Figure 257 shows a nucleotide sequence (SEQ ID NO:257) of a native sequence PRO1567 cDNA, wherein SEQ ID NO:257 is a clone designated herein as "DNA76541-1675".

15       Figure 258 shows the amino acid sequence (SEQ ID NO:258) derived from the coding sequence of SEQ ID NO:257 shown in Figure 257.

Figure 259 shows a nucleotide sequence (SEQ ID NO:259) of a native sequence PRO1600 cDNA, wherein SEQ ID NO:259 is a clone designated herein as "DNA77503-1686".

20       Figure 260 shows the amino acid sequence (SEQ ID NO:260) derived from the coding sequence of SEQ ID NO:259 shown in Figure 259.

Figure 261 shows a nucleotide sequence (SEQ ID NO:261) of a native sequence PRO1868 cDNA, wherein SEQ ID NO:261 is a clone designated herein as "DNA77624-2515".

Figure 262 shows the amino acid sequence (SEQ ID NO:262) derived from the coding sequence of SEQ ID NO:261 shown in Figure 261.

25       Figure 263 shows a nucleotide sequence (SEQ ID NO:263) of a native sequence PRO1890 cDNA, wherein SEQ ID NO:263 is a clone designated herein as "DNA79230-2525".

Figure 264 shows the amino acid sequence (SEQ ID NO:264) derived from the coding sequence of SEQ ID NO:263 shown in Figure 263.

30       Figure 265 shows a nucleotide sequence (SEQ ID NO:265) of a native sequence PRO1887 cDNA, wherein SEQ ID NO:265 is a clone designated herein as "DNA79862-2522".

Figure 266 shows the amino acid sequence (SEQ ID NO:265) derived from the coding sequence of SEQ ID NO:265 shown in Figure 265.

Figure 267 shows a nucleotide sequence (SEQ ID NO:267) of a native sequence PRO4353 cDNA, wherein SEQ ID NO:267 is a clone designated herein as "DNA80145-2594".

35       Figure 268 shows the amino acid sequence (SEQ ID NO:268) derived from the coding sequence of SEQ ID NO:267 shown in Figure 267.

Figure 269 shows a nucleotide sequence (SEQ ID NO:269) of a native sequence PRO1782 cDNA, wherein

SEQ ID NO:269 is a clone designated herein as "DNA80899-2501".

Figure 270 shows the amino acid sequence (SEQ ID NO:270) derived from the coding sequence of SEQ ID NO:269 shown in Figure 269.

5      Figure 271 shows a nucleotide sequence (SEQ ID NO:271) of a native sequence PRO1928 cDNA, wherein SEQ ID NO:271 is a clone designated herein as "DNA81754-2532".

Figure 272 shows the amino acid sequence (SEQ ID NO:272) derived from the coding sequence of SEQ ID NO:271 shown in Figure 271.

Figure 273 shows a nucleotide sequence (SEQ ID NO:273) of a native sequence PRO1865 cDNA, wherein SEQ ID NO:273 is a clone designated herein as "DNA81757-2512".

10      Figure 274 shows the amino acid sequence (SEQ ID NO:274) derived from the coding sequence of SEQ ID NO:273 shown in Figure 273.

Figure 275 shows a nucleotide sequence (SEQ ID NO:275) of a native sequence PRO4341 cDNA, wherein SEQ ID NO:275 is a clone designated herein as "DNA81761-2583".

15      Figure 276 shows the amino acid sequence (SEQ ID NO:276) derived from the coding sequence of SEQ ID NO:275 shown in Figure 275.

Figure 277 shows a nucleotide sequence (SEQ ID NO:277) of a native sequence PRO6714 cDNA, wherein SEQ ID NO:277 is a clone designated herein as "DNA82358-2738".

Figure 278 shows the amino acid sequence (SEQ ID NO:278) derived from the coding sequence of SEQ ID NO:277 shown in Figure 277.

20      Figure 279 shows a nucleotide sequence (SEQ ID NO:279) of a native sequence PRO5723 cDNA, wherein SEQ ID NO:279 is a clone designated herein as "DNA82361".

Figure 280 shows the amino acid sequence (SEQ ID NO:280) derived from the coding sequence of SEQ ID NO:279 shown in Figure 279.

25      Figure 281 shows a nucleotide sequence (SEQ ID NO:281) of a native sequence PRO3438 cDNA, wherein SEQ ID NO:281 is a clone designated herein as "DNA82364-2538".

Figure 282 shows the amino acid sequence (SEQ ID NO:282) derived from the coding sequence of SEQ ID NO:281 shown in Figure 281.

Figure 283 shows a nucleotide sequence (SEQ ID NO:283) of a native sequence PRO6071 cDNA, wherein SEQ ID NO:283 is a clone designated herein as "DNA82403-2959".

30      Figure 284 shows the amino acid sequence (SEQ ID NO:284) derived from the coding sequence of SEQ ID NO:283 shown in Figure 283.

Figure 285 shows a nucleotide sequence (SEQ ID NO:285) of a native sequence PRO1801 cDNA, wherein SEQ ID NO:285 is a clone designated herein as "DNA83500-2506".

35      Figure 286 shows the amino acid sequence (SEQ ID NO:286) derived from the coding sequence of SEQ ID NO:285 shown in Figure 285.

Figure 287 shows a nucleotide sequence (SEQ ID NO:287) of a native sequence PRO4324 cDNA, wherein SEQ ID NO:287 is a clone designated herein as "DNA83560-2569".

Figure 288 shows the amino acid sequence (SEQ ID NO:288) derived from the coding sequence of SEQ ID NO:287 shown in Figure 287.

Figure 289 shows a nucleotide sequence (SEQ ID NO:289) of a native sequence PRO4333 cDNA, wherein SEQ ID NO:289 is a clone designated herein as "DNA84210-2576".

5        Figure 290 shows the amino acid sequence (SEQ ID NO:290) derived from the coding sequence of SEQ ID NO:289 shown in Figure 289.

Figure 291 shows a nucleotide sequence (SEQ ID NO:291) of a native sequence PRO4405 cDNA, wherein SEQ ID NO:291 is a clone designated herein as "DNA84920-2614".

10       Figure 292 shows the amino acid sequence (SEQ ID NO:292) derived from the coding sequence of SEQ ID NO:291 shown in Figure 291.

Figure 293 shows a nucleotide sequence (SEQ ID NO:293) of a native sequence PRO4356 cDNA, wherein SEQ ID NO:293 is a clone designated herein as "DNA86576-2595".

Figure 294 shows the amino acid sequence (SEQ ID NO:294) derived from the coding sequence of SEQ ID NO:293 shown in Figure 293.

15       Figure 295 shows a nucleotide sequence (SEQ ID NO:295) of a native sequence PRO3444 cDNA, wherein SEQ ID NO:295 is a clone designated herein as "DNA87997".

Figure 296 shows the amino acid sequence (SEQ ID NO:296) derived from the coding sequence of SEQ ID NO:295 shown in Figure 295.

20       Figure 297 shows a nucleotide sequence (SEQ ID NO:297) of a native sequence PRO4302 cDNA, wherein SEQ ID NO:297 is a clone designated herein as "DNA92218-2554".

Figure 298 shows the amino acid sequence (SEQ ID NO:298) derived from the coding sequence of SEQ ID NO:297 shown in Figure 297.

Figure 299 shows a nucleotide sequence (SEQ ID NO:299) of a native sequence PRO4371 cDNA, wherein SEQ ID NO:299 is a clone designated herein as "DNA92233-2599".

25       Figure 300 shows the amino acid sequence (SEQ ID NO:300) derived from the coding sequence of SEQ ID NO:299 shown in Figure 299.

Figure 301 shows a nucleotide sequence (SEQ ID NO:301) of a native sequence PRO4354 cDNA, wherein SEQ ID NO:301 is a clone designated herein as "DNA92256-2596".

30       Figure 302 shows the amino acid sequence (SEQ ID NO:302) derived from the coding sequence of SEQ ID NO:301 shown in Figure 301.

Figure 303 shows a nucleotide sequence (SEQ ID NO:303) of a native sequence PRO5725 cDNA, wherein SEQ ID NO:303 is a clone designated herein as "DNA92265-2669".

Figure 304 shows the amino acid sequence (SEQ ID NO:304) derived from the coding sequence of SEQ ID NO:303 shown in Figure 303.

35       Figure 305 shows a nucleotide sequence (SEQ ID NO:305) of a native sequence PRO4408 cDNA, wherein SEQ ID NO:305 is a clone designated herein as "DNA92274-2617".

Figure 306 shows the amino acid sequence (SEQ ID NO:306) derived from the coding sequence of SEQ

ID NO:305 shown in Figure 305.

Figure 307 shows a nucleotide sequence (SEQ ID NO:307) of a native sequence PRO9940 cDNA, wherein SEQ ID NO:307 is a clone designated herein as "DNA92282".

5 Figure 308 shows the amino acid sequence (SEQ ID NO:308) derived from the coding sequence of SEQ ID NO:307 shown in Figure 307.

Figure 309 shows a nucleotide sequence (SEQ ID NO:309) of a native sequence PRO5737 cDNA, wherein SEQ ID NO:309 is a clone designated herein as "DNA92929-2534-1".

Figure 310 shows the amino acid sequence (SEQ ID NO:310) derived from the coding sequence of SEQ ID NO:309 shown in Figure 309.

10 Figure 311 shows a nucleotide sequence (SEQ ID NO:311) of a native sequence PRO4425 cDNA, wherein SEQ ID NO:311 is a clone designated herein as "DNA93011-2637".

Figure 312 shows the amino acid sequence (SEQ ID NO:312) derived from the coding sequence of SEQ ID NO:311 shown in Figure 311.

15 Figure 313 shows a nucleotide sequence (SEQ ID NO:313) of a native sequence PRO4345 cDNA, wherein SEQ ID NO:313 is a clone designated herein as "DNA94854-2586".

Figure 314 shows the amino acid sequence (SEQ ID NO:314) derived from the coding sequence of SEQ ID NO:313 shown in Figure 313.

Figure 315 shows a nucleotide sequence (SEQ ID NO:315) of a native sequence PRO4342 cDNA, wherein SEQ ID NO:315 is a clone designated herein as "DNA96787-2534-1".

20 Figure 316 shows the amino acid sequence (SEQ ID NO:316) derived from the coding sequence of SEQ ID NO:315 shown in Figure 315.

Figure 317 shows a nucleotide sequence (SEQ ID NO:317) of a native sequence PRO3562 cDNA, wherein SEQ ID NO:317 is a clone designated herein as "DNA96791".

25 Figure 318 shows the amino acid sequence (SEQ ID NO:318) derived from the coding sequence of SEQ ID NO:317 shown in Figure 317.

Figure 319 shows a nucleotide sequence (SEQ ID NO:319) of a native sequence PRO4422 cDNA, wherein SEQ ID NO:319 is a clone designated herein as "DNA96867-2620".

Figure 320 shows the amino acid sequence (SEQ ID NO:320) derived from the coding sequence of SEQ ID NO:319 shown in Figure 319.

30 Figure 321 shows a nucleotide sequence (SEQ ID NO:321) of a native sequence PRO5776 cDNA, wherein SEQ ID NO:321 is a clone designated herein as "DNA96872-2674".

Figure 322 shows the amino acid sequence (SEQ ID NO:322) derived from the coding sequence of SEQ ID NO:321 shown in Figure 321.

35 Figure 323 shows a nucleotide sequence (SEQ ID NO:323) of a native sequence PRO4430 cDNA, wherein SEQ ID NO:323 is a clone designated herein as "DNA96878-2626".

Figure 324 shows the amino acid sequence (SEQ ID NO:324) derived from the coding sequence of SEQ ID NO:323 shown in Figure 323.



Figure 325 shows a nucleotide sequence (SEQ ID NO:325) of a native sequence PRO4499 cDNA, wherein SEQ ID NO:325 is a clone designated herein as "DNA96889-2641".

Figure 326 shows the amino acid sequence (SEQ ID NO:326) derived from the coding sequence of SEQ ID NO:325 shown in Figure 325.

5        Figure 327 shows a nucleotide sequence (SEQ ID NO:327) of a native sequence PRO4503 cDNA, wherein SEQ ID NO:327 is a clone designated herein as "DNA100312-2645".

Figure 328 shows the amino acid sequence (SEQ ID NO:328) derived from the coding sequence of SEQ ID NO:327 shown in Figure 327.

10       Figure 329 shows a nucleotide sequence (SEQ ID NO:329) of a native sequence PRO10008 cDNA, wherein SEQ ID NO:329 is a clone designated herein as "DNA101921".

Figure 330 shows the amino acid sequence (SEQ ID NO:330) derived from the coding sequence of SEQ ID NO:329 shown in Figure 329.

Figure 331 shows a nucleotide sequence (SEQ ID NO:331) of a native sequence PRO5730 cDNA, wherein SEQ ID NO:331 is a clone designated herein as "DNA101926".

15       Figure 332 shows the amino acid sequence (SEQ ID NO:332) derived from the coding sequence of SEQ ID NO:331 shown in Figure 331.

Figure 333 shows a nucleotide sequence (SEQ ID NO:333) of a native sequence PRO6008 cDNA, wherein SEQ ID NO:333 is a clone designated herein as "DNA102844".

20       Figure 334 shows the amino acid sequence (SEQ ID NO:334) derived from the coding sequence of SEQ ID NO:333 shown in Figure 333.

Figure 335 shows a nucleotide sequence (SEQ ID NO:335) of a native sequence PRO4527 cDNA, wherein SEQ ID NO:335 is a clone designated herein as "DNA103197".

Figure 336 shows the amino acid sequence (SEQ ID NO:336) derived from the coding sequence of SEQ ID NO:335 shown in Figure 335.

25       Figure 337 shows a nucleotide sequence (SEQ ID NO:337) of a native sequence PRO4538 cDNA, wherein SEQ ID NO:337 is a clone designated herein as "DNA103208".

Figure 338 shows the amino acid sequence (SEQ ID NO:338) derived from the coding sequence of SEQ ID NO:337 shown in Figure 337.

30       Figure 339 shows a nucleotide sequence (SEQ ID NO:339) of a native sequence PRO4553 cDNA, wherein SEQ ID NO:339 is a clone designated herein as "DNA103223".

Figure 340 shows the amino acid sequence (SEQ ID NO:340) derived from the coding sequence of SEQ ID NO:339 shown in Figure 339.

Figure 341 shows a nucleotide sequence (SEQ ID NO:341) of a native sequence PRO6006 cDNA, wherein SEQ ID NO:341 is a clone designated herein as "DNA105782-2693".

35       Figure 342 shows the amino acid sequence (SEQ ID NO:342) derived from the coding sequence of SEQ ID NO:341 shown in Figure 341.

Figure 343 shows a nucleotide sequence (SEQ ID NO:343) of a native sequence PRO6029 cDNA, wherein

SEQ ID NO:343 is a clone designated herein as "DNA105849-2704".

Figure 344 shows the amino acid sequence (SEQ ID NO:344) derived from the coding sequence of SEQ ID NO:343 shown in Figure 343.

5 Figure 345 shows a nucleotide sequence (SEQ ID NO:345) of a native sequence PRO9821 cDNA, wherein SEQ ID NO:345 is a clone designated herein as "DNA108725-2766".

Figure 346 shows the amino acid sequence (SEQ ID NO:346) derived from the coding sequence of SEQ ID NO:345 shown in Figure 345.

Figure 347 shows a nucleotide sequence (SEQ ID NO:347) of a native sequence PRO9820 cDNA, wherein SEQ ID NO:347 is a clone designated herein as "DNA108769-2765".

10 Figure 348 shows the amino acid sequence (SEQ ID NO:348) derived from the coding sequence of SEQ ID NO:347 shown in Figure 347.

Figure 349 shows a nucleotide sequence (SEQ ID NO:349) of a native sequence PRO9771 cDNA, wherein SEQ ID NO:349 is a clone designated herein as "DNA119498-2965".

15 Figure 350 shows the amino acid sequence (SEQ ID NO:350) derived from the coding sequence of SEQ ID NO:349 shown in Figure 349.

Figure 351 shows a nucleotide sequence (SEQ ID NO:351) of a native sequence PRO7436 cDNA, wherein SEQ ID NO:351 is a clone designated herein as "DNA119535-2756".

Figure 352 shows the amino acid sequence (SEQ ID NO:352) derived from the coding sequence of SEQ ID NO:351 shown in Figure 351.

20 Figure 353 shows a nucleotide sequence (SEQ ID NO:353) of a native sequence PRO10096 cDNA, wherein SEQ ID NO:353 is a clone designated herein as "DNA125185-2806".

Figure 354 shows the amino acid sequence (SEQ ID NO:354) derived from the coding sequence of SEQ ID NO:353 shown in Figure 353.

25 Figure 355 shows a nucleotide sequence (SEQ ID NO:355) of a native sequence PRO19670 cDNA, wherein SEQ ID NO:355 is a clone designated herein as "DNA131639-2874".

Figure 356 shows the amino acid sequence (SEQ ID NO:356) derived from the coding sequence of SEQ ID NO:355 shown in Figure 355.

Figure 357 shows a nucleotide sequence (SEQ ID NO:357) of a native sequence PRO20044 cDNA, wherein SEQ ID NO:357 is a clone designated herein as "DNA139623-2893".

30 Figure 358 shows the amino acid sequence (SEQ ID NO:358) derived from the coding sequence of SEQ ID NO:357 shown in Figure 357.

Figure 359 shows a nucleotide sequence (SEQ ID NO:359) of a native sequence PRO9873 cDNA, wherein SEQ ID NO:359 is a clone designated herein as "DNA143076-2787".

35 Figure 360 shows the amino acid sequence (SEQ ID NO:360) derived from the coding sequence of SEQ ID NO:359 shown in Figure 359.

Figure 361 shows a nucleotide sequence (SEQ ID NO:361) of a native sequence PRO21366 cDNA, wherein SEQ ID NO:361 is a clone designated herein as "DNA143276-2975".

Figure 362 shows the amino acid sequence (SEQ ID NO:362) derived from the coding sequence of SEQ ID NO:361 shown in Figure 361.

Figure 363 shows a nucleotide sequence (SEQ ID NO:363) of a native sequence PRO20040 cDNA, wherein SEQ ID NO:363 is a clone designated herein as "DNA164625-2890".

5        Figure 364 shows the amino acid sequence (SEQ ID NO:364) derived from the coding sequence of SEQ ID NO:363 shown in Figure 363.

Figure 365 shows a nucleotide sequence (SEQ ID NO:365) of a native sequence PRO21184 cDNA, wherein SEQ ID NO:365 is a clone designated herein as "DNA167678-2963".

10       Figure 366 shows the amino acid sequence (SEQ ID NO:366) derived from the coding sequence of SEQ ID NO:365 shown in Figure 365.

Figure 367 shows a nucleotide sequence (SEQ ID NO:367) of a native sequence PRO21055 cDNA, wherein SEQ ID NO:367 is a clone designated herein as "DNA170021-2923".

Figure 368 shows the amino acid sequence (SEQ ID NO:368) derived from the coding sequence of SEQ ID NO:367 shown in Figure 367.

15       Figure 369 shows a nucleotide sequence (SEQ ID NO:369) of a native sequence PRO28631 cDNA, wherein SEQ ID NO:369 is a clone designated herein as "DNA170212-3000".

Figure 370 shows the amino acid sequence (SEQ ID NO:370) derived from the coding sequence of SEQ ID NO:369 shown in Figure 369.

20       Figure 371 shows a nucleotide sequence (SEQ ID NO:371) of a native sequence PRO21384 cDNA, wherein SEQ ID NO:371 is a clone designated herein as "DNA177313-2982".

Figure 372 shows the amino acid sequence (SEQ ID NO:372) derived from the coding sequence of SEQ ID NO:371 shown in Figure 371.

Figure 373 shows a nucleotide sequence (SEQ ID NO:373) of a native sequence PRO1449 cDNA, wherein SEQ ID NO:373 is a clone designated herein as "DNA64908-1163-1".

25       Figure 374 shows the amino acid sequence (SEQ ID NO:374) derived from the coding sequence of SEQ ID NO:373 shown in Figure 373.

Figure 375 shows wholemount in situ hybridization results on mouse embryos using a mouse orthologue of PRO1449 which has about 78% amino acid identity with PRO1449. The results show that PRO1449 orthologue is expressed in the developing vasculature. The cross-section further shows expression in endothelial cells and progenitors of endothelial cells.

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Figure 376 shows that a PRO1449 orthologue having about 78% amino acid identity with PRO1449 is expressed in vasculature of many inflamed and diseased tissues, but is very low, or lacking, in normal adult vessels.

Figure 377 shows that a PRO1449 orthologue having about 78% amino acid identity with PRO1449 induces ectopic vessels in the eyes of chicken embryos.

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## 5. Detailed Description of the Invention

### 5.1. Definitions

The phrases "cardiovascular, endothelial and angiogenic disorder", "cardiovascular, endothelial and angiogenic dysfunction", "cardiovascular, endothelial or angiogenic disorder" and "cardiovascular, endothelial or angiogenic dysfunction" are used interchangeably and refer in part to systemic disorders that affect vessels, such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins, and/or lymphatics. This would include indications that stimulate angiogenesis and/or cardiovascularization, and those that inhibit angiogenesis and/or cardiovascularization. Such disorders include, for example, arterial disease, such as atherosclerosis, hypertension, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, cancer such as vascular tumors, e.g., hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma, tumor angiogenesis, trauma such as wounds, burns, and other injured tissue, implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. This would also include angina, myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as CHF.

"Hypertrophy", as used herein, is defined as an increase in mass of an organ or structure independent of natural growth that does not involve tumor formation. Hypertrophy of an organ or tissue is due either to an increase in the mass of the individual cells (true hypertrophy), or to an increase in the number of cells making up the tissue (hyperplasia), or both. Certain organs, such as the heart, lose the ability to divide shortly after birth. Accordingly, "cardiac hypertrophy" is defined as an increase in mass of the heart, which, in adults, is characterized by an increase in myocyte cell size and contractile protein content without concomitant cell division. The character of the stress responsible for inciting the hypertrophy, (e.g., increased preload, increased afterload, loss of myocytes, as in myocardial infarction, or primary depression of contractility), appears to play a critical role in determining the nature of the response. The early stage of cardiac hypertrophy is usually characterized morphologically by increases in the size of myofibrils and mitochondria, as well as by enlargement of mitochondria and nuclei. At this stage, while muscle cells are larger than normal, cellular organization is largely preserved. At a more advanced stage of cardiac hypertrophy, there are preferential increases in the size or number of specific organelles, such as mitochondria, and new contractile elements are added in localized areas of the cells, in an irregular manner. Cells subjected to long-standing hypertrophy show more obvious disruptions in cellular organization, including markedly enlarged nuclei with highly lobulated membranes, which displace adjacent myofibrils and cause breakdown of normal Z-band registration. The phrase "cardiac hypertrophy" is used to include all stages of the progression of this condition, characterized by various degrees of structural damage of the heart muscle, regardless of the underlying cardiac disorder. Hence, the term also includes physiological conditions instrumental in the development of cardiac hypertrophy, such as elevated blood pressure, aortic stenosis, or myocardial infarction.

"Heart failure" refers to an abnormality of cardiac function where the heart does not pump blood at the rate

needed for the requirements of metabolizing tissues. The heart failure can be caused by a number of factors, including ischemic, congenital, rheumatic, or idiopathic forms.

“Congestive heart failure” (CHF) is a progressive pathologic state where the heart is increasingly unable to supply adequate cardiac output (the volume of blood pumped by the heart over time) to deliver the oxygenated blood to peripheral tissues. As CHF progresses, structural and hemodynamic damages occur. While these damages have a variety of manifestations, one characteristic symptom is ventricular hypertrophy. CHF is a common end result of a number of various cardiac disorders.

“Myocardial infarction” generally results from atherosclerosis of the coronary arteries, often with superimposed coronary thrombosis. It may be divided into two major types: transmural infarcts, in which myocardial necrosis involves the full thickness of the ventricular wall, and subendocardial (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both, without extending all the way through the ventricular wall to the epicardium. Myocardial infarction is known to cause both a change in hemodynamic effects and an alteration in structure in the damaged and healthy zones of the heart. Thus, for example, myocardial infarction reduces the maximum cardiac output and the stroke volume of the heart. Also associated with myocardial infarction is a stimulation of the DNA synthesis occurring in the interstice as well as an increase in the formation of collagen in the areas of the heart not affected.

As a result of the increased stress or strain placed on the heart in prolonged hypertension due, for example, to the increased total peripheral resistance, cardiac hypertrophy has long been associated with “hypertension”. A characteristic of the ventricle that becomes hypertrophic as a result of chronic pressure overload is an impaired diastolic performance. Fouad *et al.*, J. Am. Coll. Cardiol., 4: 1500-1506 (1984); Smith *et al.*, J. Am. Coll. Cardiol., 5: 869-874 (1985). A prolonged left ventricular relaxation has been detected in early essential hypertension, in spite of normal or supranormal systolic function. Hartford *et al.*, Hypertension, 6: 329-338 (1984). However, there is no close parallelism between blood pressure levels and cardiac hypertrophy. Although improvement in left ventricular function in response to antihypertensive therapy has been reported in humans, patients variously treated with a diuretic (hydrochlorothiazide), a  $\beta$ -blocker (propranolol), or a calcium channel blocker (diltiazem), have shown reversal of left ventricular hypertrophy, without improvement in diastolic function. Inouye *et al.*, Am. J. Cardiol., 53: 1583-7 (1984).

Another complex cardiac disease associated with cardiac hypertrophy is “hypertrophic cardiomyopathy”. This condition is characterized by a great diversity of morphologic, functional, and clinical features (Maron *et al.*, N. Engl. J. Med., 316: 780-789 (1987); Spirito *et al.*, N. Engl. J. Med., 320: 749-755 (1989); Louie and Edwards, Prog. Cardiovasc. Dis., 36: 275-308 (1994); Wigle *et al.*, Circulation, 92: 1680-1692 (1995)), the heterogeneity of which is accentuated by the fact that it afflicts patients of all ages. Spirito *et al.*, N. Engl. J. Med., 336: 775-785 (1997). The causative factors of hypertrophic cardiomyopathy are also diverse and little understood. In general, mutations in genes encoding sarcomeric proteins are associated with hypertrophic cardiomyopathy. Recent data suggest that  $\beta$ -myosin heavy chain mutations may account for approximately 30 to 40 percent of cases of familial hypertrophic cardiomyopathy. Watkins *et al.*, N. Engl. J. Med., 326: 1108-1114 (1992); Schwartz *et al.*, Circulation, 91: 532-540 (1995); Marian and Roberts, Circulation, 92: 1336-1347 (1995); Thierfelder *et al.*, Cell, 77: 701-712

(1994); Watkins *et al.*, Nat. Gen., 11: 434-437 (1995). Besides  $\beta$ -myosin heavy chain, other locations of genetic mutations include cardiac troponin T, alpha topomyosin, cardiac myosin binding protein C, essential myosin light chain, and regulatory myosin light chain. See, Malik and Watkins, Curr. Opin. Cardiol., 12: 295-302 (1997).

Supravalvular "aortic stenosis" is an inherited vascular disorder characterized by narrowing of the ascending aorta, but other arteries, including the pulmonary arteries, may also be affected. Untreated aortic stenosis may lead to increased intracardiac pressure resulting in myocardial hypertrophy and eventually heart failure and death. The pathogenesis of this disorder is not fully understood, but hypertrophy and possibly hyperplasia of medial smooth muscle are prominent features of this disorder. It has been reported that molecular variants of the elastin gene are involved in the development and pathogenesis of aortic stenosis. U.S. Patent No. 5,650,282 issued July 22, 1997.

"Valvular regurgitation" occurs as a result of heart diseases resulting in disorders of the cardiac valves. Various diseases, like rheumatic fever, can cause the shrinking or pulling apart of the valve orifice, while other diseases may result in endocarditis, an inflammation of the endocardium or lining membrane of the atrioventricular orifices and operation of the heart. Defects such as the narrowing of the valve stenosis or the defective closing of the valve result in an accumulation of blood in the heart cavity or regurgitation of blood past the valve. If uncorrected, prolonged valvular stenosis or insufficiency may result in cardiac hypertrophy and associated damage to the heart muscle, which may eventually necessitate valve replacement.

The treatment of all these, and other cardiovascular, endothelial and angiogenic disorders, which may or may not be accompanied by cardiac hypertrophy, is encompassed by the present invention.

The terms "cancer", "cancerous", and "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma including adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's and non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer such as hepatic carcinoma and hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and various types of head and neck cancer. The preferred cancers for treatment herein are breast, colon, lung, melanoma, ovarian, and others involving vascular tumors as noted above.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.*,  $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{90}\text{Y}$ , and  $^{186}\text{Re}$ ), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents, folic acid antagonists, anti-metabolites of nucleic acid metabolism, antibiotics, pyrimidine analogs, 5-fluorouracil, cisplatin, purine nucleosides, amines, amino acids, triazol nucleosides, or corticosteroids. Specific examples include Adriamycin, Doxorubicin, 5-Fluorouracil,

Cytosine arabinoside ("Ara-C"), Cyclophosphamide, Thiotepa, Busulfan, Cytosin, Taxol, Toxotere, Methotrexate, Cisplatin, Melphalan, Vinblastine, Bleomycin, Etoposide, Ifosfamide, Mitomycin C, Mitoxantrone, Vincristine, Vinorelbine, Carboplatin, Teniposide, Daunomycin, Carminomycin, Aminopterin, Dactinomycin, Mitomycins, Esperamicins (*see* U.S. Pat. No. 4,675,187), Melphalan, and other related nitrogen mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors, such as tamoxifen and onapristone.

A "growth-inhibitory agent" when used herein refers to a compound or composition that inhibits growth of a cell, such as an Wnt-overexpressing cancer cell, either *in vitro* or *in vivo*. Thus, the growth-inhibitory agent is one which significantly reduces the percentage of malignant cells in S phase. Examples of growth-inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami *et al.* (WB Saunders: Philadelphia, 1995), especially p. 13. Additional examples include tumor necrosis factor (TNF), an antibody capable of inhibiting or neutralizing the angiogenic activity of acidic or basic FGF or hepatocyte growth factor (HGF), an antibody capable of inhibiting or neutralizing the coagulant activities of tissue factor, protein C, or protein S (*see*, WO 91/01753, published 21 February 1991), or an antibody capable of binding to HER2 receptor (WO 89/06692), such as the 4D5 antibody (and functional equivalents thereof) (*e.g.*, WO 92/22653).

"Treatment" is an intervention performed with the intention of preventing the development or altering the pathology of a cardiovascular, endothelial, and angiogenic disorder. The concept of treatment is used in the broadest sense, and specifically includes the prevention (prophylaxis), moderation, reduction, and curing of cardiovascular, endothelial, and angiogenic disorders of any stage. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) or ameliorate a cardiovascular, endothelial, and angiogenic disorder such as hypertrophy. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. The disorder may result from any cause, including idiopathic, cardiotrophic, or myotrophic causes, or ischemia or ischemic insults, such as myocardial infarction.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial effect, such as an anti-hypertrophic effect, for an extended period of time.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, pigs, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

The phrase "cardiovascular, endothelial or angiogenic agents" refers generically to any drug that acts in treating cardiovascular, endothelial, and angiogenic disorders. Examples of cardiovascular agents are those that promote vascular homeostasis by modulating blood pressure, heart rate, heart contractility, and endothelial and smooth muscle biology, all of which factors have a role in cardiovascular disease. Specific examples of these include angiotensin-II receptor antagonists; endothelin receptor antagonists such as, for example, BOSENTAN<sup>TM</sup> and MOXONODIN<sup>TM</sup>; interferon-gamma (IFN- $\gamma$ ); des-aspartate-angiotensin I; thrombolytic agents, *e.g.*, streptokinase, urokinase, t-PA, and a t-PA variant specifically designed to have longer half-life and very high fibrin specificity, TNK t-PA (a T103N, N117Q, KHRR(296-299)AAAA t-PA variant, Keyt *et al.*, Proc. Natl. Acad. Sci. USA, 91: 3670-3674 (1994)); inotropic or hypertensive agents such as digoxigenin and  $\beta$ -adrenergic receptor blocking agents, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, and carvedilol; angiotensin converting enzyme (ACE) inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, and lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, and indapamide; and calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, nicardipine. One preferred category of this type is a therapeutic agent used for the treatment of cardiac hypertrophy or of a physiological condition instrumental in the development of cardiac hypertrophy, such as elevated blood pressure, aortic stenosis, or myocardial infarction.

"Angiogenic agents" and "endothelial agents" are active agents that promote angiogenesis and/or endothelial cell growth, or, if applicable, vasculogenesis. This would include factors that accelerate wound healing, such as growth hormone, insulin-like growth factor-I (IGF-I), VEGF, VIGF, PDGF, epidermal growth factor (EGF), CTGF and members of its family, FGF, and TGF- $\alpha$  and TGF- $\beta$ .

"Angiostatic agents" are active agents that inhibit angiogenesis or vasculogenesis or otherwise inhibit or prevent growth of cancer cells. Examples include antibodies or other antagonists to angiogenic agents as defined above, such as antibodies to VEGF. They additionally include cytotherapeutic agents such as cytotoxic agents, chemotherapeutic agents, growth-inhibitory agents, apoptotic agents, and other agents to treat cancer, such as anti-HER-2, anti-CD20, and other bioactive and organic chemical agents.

In a pharmacological sense, in the context of the present invention, a "therapeutically effective amount" of an active agent such as a PRO polypeptide or agonist or antagonist thereto or an anti-PRO antibody, refers to an amount effective in the treatment of a cardiovascular, endothelial or angiogenic disorder in a mammal and can be determined empirically.

As used herein, an "effective amount" of an active agent such as a PRO polypeptide or agonist or antagonist thereto or an anti-PRO antibody, refers to an amount effective for carrying out a stated purpose, wherein such amounts may be determined empirically for the desired effect.

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (*i.e.*, PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein



may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen *et al.*, Prot. Eng., 10:1-6 (1997) and von Heinje *et al.*, Nucl. Acids Res., 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed

herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150 or 200 amino acids in length and alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in a PRO sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program

ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations, Tables 2-3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO".

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov>, or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

In addition, % amino acid sequence identity may also be determined using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acids residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (*i.e.*, the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an amino acid sequence A which

has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 450, or 600 nucleotides in length and alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to the PRO polypeptide-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in a PRO polypeptide-encoding nucleic acid sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % nucleic acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that

has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4-5 demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA".

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In addition, % nucleic acid sequence identity values may also be generated using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % nucleic acid sequence identity value is determined by dividing (a)

the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (*i.e.*, the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding the full-length PRO polypeptide as shown in the specification herein and accompanying figures. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated", when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide is free of association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" nucleic acid molecule encoding a PRO polypeptide or an "isolated" nucleic acid molecule encoding an anti-PRO antibody is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the PRO-encoding nucleic acid or the natural source of the anti-PRO-encoding nucleic acid. Preferably, the isolated nucleic acid is free of association with all components with which it is naturally associated. An isolated PRO-encoding nucleic acid molecule or an isolated anti-PRO-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the PRO-encoding nucleic acid molecule or from the anti-PRO-encoding nucleic acid molecule as it exists in natural cells. However, an isolated nucleic acid molecule encoding a PRO polypeptide or an isolated nucleic acid molecule encoding an anti-PRO antibody includes PRO-nucleic acid molecules or anti-PRO-nucleic acid molecules contained in cells that ordinarily express PRO polypeptides or anti-PRO antibodies where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked

coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize, for example, promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a PRO polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in the same reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature that can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, *see*, Ausubel *et al.*, Current Protocols in Molecular Biology (Wiley Interscience Publishers, 1995).

"Stringent conditions" or "high-stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example, 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately-stringent conditions" may be identified as described by Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Press, 1989), and include the use of washing solution and hybridization conditions (*e.g.*, temperature, ionic strength, and % SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters

in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The modifier "epitope-tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

"Active" or "activity" in the context of PRO variants refers to form(s) of PRO proteins that retain the biologic and/or immunologic activities of a native or naturally-occurring PRO polypeptide.

"Biological activity" in the context of a molecule that antagonizes a PRO polypeptide that can be identified by the screening assays disclosed herein (*e.g.*, an organic or inorganic small molecule, peptide, etc.) is used to refer to the ability of such molecules to bind or complex with the PRO polypeptide identified herein, or otherwise interfere with the interaction of the PRO polypeptide with other cellular proteins or otherwise inhibits the transcription or translation of the PRO polypeptide. Particularly preferred biological activity includes cardiac hypertrophy, activity that acts on systemic disorders that affect vessels, such as diabetes mellitus, as well as diseases of the arteries, capillaries, veins, and/or lymphatics, and cancer.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes one or more of the biological activities of a native PRO polypeptide disclosed herein, for example, if applicable, its mitogenic or angiogenic activity. Antagonists of a PRO polypeptide may act by interfering with the binding of a PRO polypeptide to a cellular receptor, by incapacitating or killing cells that have been activated by a PRO polypeptide, or by interfering with vascular endothelial cell activation after binding of a PRO polypeptide to a cellular receptor. All such points of intervention by a PRO polypeptide antagonist shall be considered equivalent for purposes of this invention. The antagonists inhibit the mitogenic, angiogenic, or other biological activity of PRO polypeptides, and thus are useful for the treatment of diseases or disorders characterized by undesirable excessive neovascularization, including by way of example tumors, and especially solid malignant tumors, rheumatoid arthritis, psoriasis, atherosclerosis, diabetic and other retinopathies, retrolental fibroplasia, age-related macular degeneration, neovascular glaucoma, hemangiomas, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, and chronic inflammation. The antagonists also are useful for the treatment of diseases or disorders characterized by undesirable excessive vascular permeability, such as edema associated with brain tumors, ascites associated with malignancies, Meigs' syndrome, lung inflammation, nephrotic syndrome, pericardial effusion (such as that associated with pericarditis), and pleural effusion. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments, or amino acid sequence variants of native PRO polypeptides, peptides, small organic molecules, etc.

A "small molecule" is defined herein to have a molecular weight below about 500 daltons.



The term "PRO polypeptide receptor" as used herein refers to a cellular receptor for a PRO polypeptide, ordinarily a cell-surface receptor found on vascular endothelial cells, as well as variants thereof that retain the ability to bind a PRO polypeptide.

"Antibodies" (Abs) and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas. The term "antibody" is used in the broadest sense and specifically covers, without limitation, intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies) formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity.

"Native antibodies" and "native immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain ( $V_H$ ) followed by a number of constant domains. Each light chain has a variable domain at one end ( $V_L$ ) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains.

The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody to and for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a  $\beta$ -sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the  $\beta$ -sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies. See, Kabat *et al.*, NIH Publ. No.91-3242, Vol. I, pages 647-669 (1991). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies (Zapata *et al.*, Protein Eng., 8(10): 1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize

readily. Pepsin treatment yields an  $F(ab')_2$  fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the  $V_H$ - $V_L$  dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group.  $F(ab')_2$  antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa ( $\kappa$ ) and lambda ( $\lambda$ ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM; and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called  $\alpha$ ,  $\delta$ ,  $\epsilon$ ,  $\gamma$ , and  $\mu$ , respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.*, Nature, 256: 495 (1975), or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, Nature, 352: 624-628 (1991) and Marks *et al.*, J. Mol. Biol., 222: 581-597 (1991), for example.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. U.S. Patent No. 4,816,567; Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81: 6851-6855 (1984).

"Humanized" forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub>, or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and maximize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody preferably also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, *see* Jones *et al.*, Nature, 321: 522-525 (1986); Reichmann *et al.*, Nature, 332: 323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2: 593-596 (1992). The humanized antibody includes a PRIMATIZED™ antibody wherein the antigen-binding region of the antibody is derived from an antibody produced by immunizing macaque monkeys with the antigen of interest.

"Single-chain Fv" or "sFv" antibody fragments comprise the V<sub>H</sub> and V<sub>L</sub> domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V<sub>H</sub> and V<sub>L</sub> domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv *see*, Pluckthun in The Pharmacology of Monoclonal Antibodies, Vol. 113, Rosenberg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) in the same polypeptide chain (V<sub>H</sub> - V<sub>L</sub>). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

An "isolated" antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere

with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells, since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or other composition that is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g., radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable. Radionuclides that can serve as detectable labels include, for example, I-131, I-123, I-125, Y-90, Re-188, At-211, Cu-67, Bi-212, and Pd-109. The label may also be a non-detectable entity such as a toxin.

By "solid phase" is meant a non-aqueous matrix to which an antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant that is useful for delivery of a drug (such as the PRO polypeptide or antibodies thereto disclosed herein) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

As used herein, the term "immunoadhesin" designates antibody-like molecules that combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity that is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD, or IgM.

As shown below, Table 1 provides the complete source code for the ALIGN-2 sequence comparison computer program. This source code may be routinely compiled for use on a UNIX operating system to provide

the ALIGN-2 sequence comparison computer program.

In addition, Tables 2-5 show hypothetical exemplifications for using the below described method to determine % amino acid sequence identity (Tables 2-3) and % nucleic acid sequence identity (Tables 4-5) using the ALIGN-2 sequence comparison computer program, wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, "X", "Y", and "Z" each represent different hypothetical amino acid residues and "N", "L" and "V" each represent different hypothetical nucleotides.

Table 1

```

/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
 * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define _M      -8      /* value of a match with a stop */

int _day[26][26] = {
/* A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */ { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */ { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */ { -2, -4, 15, -5, -5, -4, -3, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
/* D */ { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */ { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
/* F */ { -4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */ { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */ { -1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
/* I */ { -1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */ { -1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */ { -2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */ { -1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
/* N */ { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */ { _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */ { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */ { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */ { -2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
/* S */ { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
/* T */ { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */ { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
/* W */ { -6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
/* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */ { -3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */ { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

```

**Table 1 (cont')**

```

/*
*/
#include <stdio.h>
#include <ctype.h>

#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
#define MX          4       /* save if there's at least MX-1 bases since last jmp */

#define DMAT        3       /* value of matching bases */
#define DMIS        0       /* penalty for mismatched bases */
#define DINS0       8       /* penalty for a gap */
#define DINS1       1       /* penalty per base */
#define PINS0       8       /* penalty for a gap */
#define PINS1       4       /* penalty per residue */

struct jmp {
    short          n[MAXJMP];    /* size of jmp (neg for dely) */
    unsigned short x[MAXJMP];    /* base no. of jmp in seq x */
};                               /* limits seq to 2^16 -1 */

struct diag {
    int            score;        /* score at last jmp */
    long           offset;       /* offset of prev block */
    short          jmp;         /* current jmp index */
    struct jmp     jp;          /* list of jmps */
};

struct path {
    int            spc;          /* number of leading spaces */
    short          n[JMPS];      /* size of jmp (gap) */
    int            x[JMPS];      /* loc of jmp (last elem before gap) */
};

char              *ofile;       /* output file name */
char              *namex[2];     /* seq names: getseqs( ) */
char              *prog;        /* prog name for err msgs */
char              *seqx[2];      /* seqs: getseqs( ) */
int               dmax;         /* best diag: nw( ) */
int               dmax0;        /* final diag */
int               dna;          /* set if dna: main( ) */
int               endgaps;       /* set if penalizing end gaps */
int               gapx, gapy;    /* total gaps in seqs */
int               len0, len1;    /* seq lens */
int               ngapx, ngapy;  /* total size of gaps */
int               smax;         /* max score: nw( ) */
int               *xbm;         /* bitmap for matching */
long              offset;       /* current offset in jmp file */
struct            diag          *dx;    /* holds diagonals */
struct            path          pp[2];  /* holds path for seqs */

char              *calloc( ), *malloc( ), *index( ), *strcpy( );
char              *getseq( ), *g_calloc( );

```

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
* The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
* Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
#include "nw.h"
#include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
    1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
    1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
int      ac;
char     *av[];
{
    prog = av[0];
    if (ac != 3) {
        fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';', '>' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0; /* 1 to penalize endgaps */
    ofile = "align.out"; /* output file */

    nw(); /* fill in the matrix, get the possible jumps */
    readjumps(); /* get the actual jumps */
    print(); /* print stats, alignment */

    cleanup(0); /* unlink any tmp files */
}

```

main



**Table 1 (cont')**

```

/* do the alignment, return best score: main( )
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw( )
{
    char      *px, *py;           /* seqs and ptrs */
    int      *ndely, *dely;       /* keep track of dely */
    int      ndelx, delx;         /* keep track of delx */
    int      *tmp;                /* for swapping row0, row1 */
    int      mis;                 /* score for each type */
    int      ins0, ins1;          /* insertion penalties */
    register id;                  /* diagonal index */
    register ij;                  /* jmp index */
    register *col0, *col1;        /* score for curr, last row */
    register xx, yy;              /* index into seqs */

    dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

    ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
    dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
    col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
    col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
    ins0 = (dna)? DINS0 : PINS0;
    ins1 = (dna)? DINS1 : PINS1;

    smax = -10000;
    if (endgaps) {
        for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
            col0[yy] = dely[yy] = col0[yy-1] - ins1;
            ndely[yy] = yy;
        }
        col0[0] = 0;          /* Waterman Bull Math Biol 84 */
    }
    else
        for (yy = 1; yy <= len1; yy++)
            dely[yy] = -ins0;

    /* fill in match matrix
     */
    for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
        /* initialize first entry in col
         */
        if (endgaps) {
            if (xx == 1)
                col1[0] = delx = -(ins0+ins1);
            else
                col1[0] = delx = col0[0] - ins1;
            ndelx = xx;
        }
        else {
            col1[0] = 0;
            delx = -ins0;
            ndelx = 0;
        }
    }
}

```

nw

**Table 1 (cont')**

...nw

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongong del
     */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */

```

**Table 1 (cont')**

...nw

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
    col1[yy] = mis;
else if (delx >= dely[yy]) {
    col1[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
    && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
        dx[id].jp.n[ij] = ndelx;
        dx[id].jp.x[ij] = xx;
        dx[id].score = delx;
    }
} else {
    col1[yy] = dely[yy];
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
    && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejumps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
        dx[id].jp.n[ij] = -ndely[yy];
        dx[id].jp.x[ij] = xx;
        dx[id].score = dely[yy];
    }
}
if (xx == len0 && yy < len1) {
    /* last col
    */
    if (endgaps)
        col1[yy] -= ins0+ins1*(len1-yy);
    if (col1[yy] > smax) {
        smax = col1[yy];
        dmax = id;
    }
}
}
if (endgaps && xx < len0)
    col1[yy-1] -= ins0+ins1*(len0-xx);
if (col1[yy-1] > smax) {
    smax = col1[yy-1];
    dmax = id;
}
tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)col1);
}

```

Table 1 (cont')

```

/*
 *
 * print() -- only routine visible outside this module
 *
 * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 * nums() -- put out a number line: dumpblock()
 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

#include "nw.h"

#define SPC 3
#define P_LINE 256 /* maximum output line */
#define P_SPC 3 /* space between name or num and seq */

extern _day[26][26];
int olen; /* set output line length */
FILE *fx; /* output file */

print()
{
    int lx, ly, firstgap, lastgap; /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
        fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
        pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

```

**print**

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
getmat(lx, ly, firstgap, lastgap)                                     getmat
{
    int      lx, ly;
    int      firstgap, lastgap;
    /* "core" (minus endgaps) */
    /* leading trailing overlap */

    int      nm, i0, i1, siz0, siz1;
    char      outx[32];
    double    pct;
    register  n0, n1;
    register char *p0, *p1;

    /* get total matches, score
    */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
    n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;

    nm = 0;
    while ( *p0 && *p1 ) {
        if (siz0) {
            p1++;
            n1++;
            siz0--;
        }
        else if (siz1) {
            p0++;
            n0++;
            siz1--;
        }
        else {
            if (xbrn[*p0-'A']&xbrn[*p1-'A'])
                nm++;
            if (n0++ == pp[0].x[i0])
                siz0 = pp[0].n[i0++];
            if (n1++ == pp[1].x[i1])
                siz1 = pp[1].n[i1++];
            p0++;
            p1++;
        }
    }

    /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
    */
    if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
    pct = 100.*(double)nm/(double)lx;
    fprintf(fx, "\n");
    fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? "" : "es", lx, pct);
}

```

**Table 1 (cont')**

```

fprintf(fx, "< gaps in first sequence: %d", gapx);
if (gapx) {
    (void) sprintf(outx, "(%d %s%s)",
        ngapx, (dna)? "base":"residue", (ngapx == 1)? ":" : "s");
    fprintf(fx, "%s", outx);

    fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, "(%d %s%s)",
            ngapy, (dna)? "base":"residue", (ngapy == 1)? ":" : "s");
        fprintf(fx, "%s", outx);
    }
    if (dna)
        fprintf(fx,
            "\n< score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);
    else
        fprintf(fx,
            "\n< score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
        fprintf(fx,
            "< endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
            firstgap, (dna)? "base" : "residue", (firstgap == 1)? ":" : "s",
            lastgap, (dna)? "base" : "residue", (lastgap == 1)? ":" : "s");
    else
        fprintf(fx, "< endgaps not penalized\n");
}

static      nm;           /* matches in core -- for checking */
static      lmax;         /* lengths of stripped file names */
static      ij[2];        /* jmp index for a path */
static      nc[2];        /* number at start of current line */
static      ni[2];        /* current elem number -- for gapping */
static      siz[2];
static char  *ps[2];       /* ptr to current element */
static char  *po[2];       /* ptr to next output char slot */
static char  out[2][P_LINE]; /* output line */
static char  star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp[]
 */
static
pr_align()
{
    int      nn;           /* char count */
    int      more;
    register i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(namex[i]);
        if (nn > lmax)
            lmax = nn;

        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
        po[i] = out[i];
    }
}

```

...getmat

pr\_align

**Table 1 (cont')****...pr\_align**

```

for (nn = nm = 0, more = 1; more; ) {
    for (i = more = 0; i < 2; i++) {
        /*
         * do we have more of this sequence?
         */
        if (!*ps[i])
            continue;

        more++;

        if (pp[i].spc) { /* leading space */
            *po[i]++ = ' ';
            pp[i].spc--;
        }
        else if (siz[i]) { /* in a gap */
            *po[i]++ = '-';
            siz[i]--;
        }
        else { /* we're putting a seq element
                */
            *po[i] = *ps[i];
            if (islower(*ps[i]))
                *ps[i] = toupper(*ps[i]);

            po[i]++;
            ps[i]++;

            /*
             * are we at next gap for this seq?
             */
            if (ni[i] == pp[i].x[ij[i]]) {
                /*
                 * we need to merge all gaps
                 * at this location
                 */
                siz[i] = pp[i].n[ij[i]] + +;
                while (ni[i] == pp[i].x[ij[i]])
                    siz[i] += pp[i].n[ij[i]] + +;
            }
            ni[i]++;
        }
    }
    if (++nn == olen || !more && nn) {
        dumpblock();
        for (i = 0; i < 2; i++)
            po[i] = out[i];
        nn = 0;
    }
}

/*
 * dump a block of lines, including numbers, stars: pr_align( )
 */
static
dumpblock( )
{
    register i;

    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';
}

```

**dumpblock**

Table 1 (cont')

...dumpblock

```

(void) putc('\n', fx);
for (i = 0; i < 2; i++) {
    if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
        if (i == 0)
            nums(i);
        if (i == 0 && *out[1])
            stars( );
        putline(i);
        if (i == 0 && *out[1])
            fprintf(fx, star);
        if (i == 1)
            nums(i);
    }
}

/*
 * put out a number line: dumpblock( )
 */
static
nums(ix)
int ix; /* index in out[] holding seq line */
{
    char nline[P_LINE];
    register i, j;
    register char *pn, *px, *py;

    for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
        *pn = ' ';
    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
        if (*py == ' ' || *py == '-')
            *pn = ' ';
        else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
                for (px = pn; j; j /= 10, px--)
                    *px = j%10 + '0';
                if (i < 0)
                    *px = '-';
            }
            else
                *pn = ' ';
            i++;
        }
    }
    *pn = '\0';
    nc[ix] = i;
    for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
    (void) putc('\n', fx);
}

/*
 * put out a line (name, [num], seq, [num]): dumpblock( )
 */
static
putline(ix)
int ix;
{

```

nums

putline



Table 1 (cont')

...putline

```

int          i;
register char *px;

for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
    (void) putc(*px, fx);
for (; i < lmax+P_SPC; i++)
    (void) putc(' ', fx);

/* these count from 1:
 * ni[] is current element (from 1)
 * nc[] is number at start of current line
 */
for (px = out[ix]; *px; px++)
    (void) putc(*px&0x7F, fx);
(void) putc('\n', fx);
}

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock( )
 */
static
stars( )
{
    int          i;
    register char *p0, *p1, cx, *px;

    if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
        !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
        return;
    px = star;
    for (i = lmax+P_SPC; i; i--)
        *px++ = ' ';

    for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
        if (isalpha(*p0) && isalpha(*p1)) {
            if (xbm[*p0-'A']&xbm[*p1-'A']) {
                cx = '*';
                nm++;
            }
            else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                cx = '.';
            else
                cx = ' ';
        }
        else
            cx = ' ';
        *px++ = cx;
    }
    *px++ = '\n';
    *px = '\0';
}

```

stars

**Table 1 (cont')**

```

/*
 * strip path or prefix from pn, return len: pr_align( )
 */
static
stripname(pn)                                stripname
char      *pn;      /* file name (may be path) */
{
    register char      *px, *py;

    py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
    if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}

```

**Table 1 (cont')**

```

/*
 * cleanup( ) -- cleanup any tmp file
 * getseq( ) -- read in seq, set dna, len, maxlen
 * g_calloc( ) -- calloc( ) with error checkin
 * readjumps( ) -- get the good jumps, from tmp file if necessary
 * writejumps( ) -- write a filled array of jumps to a tmp file: nw( )
 */
#include "nw.h"
#include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";          /* tmp file for jumps */
FILE    *fj;

int      cleanup( );                          /* cleanup tmp file */
long     lseek( );

/*
 * remove any tmp file if we blow
 */
cleanup(i)                                     cleanup
{
    int    i;
    if (fj)
        (void) unlink(jname);
    exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
getseq(file, len)                             getseq
{
    char    *file;    /* file name */
    int     *len;     /* seq len */

    char    line[1024], *pseq;
    register char *px, *py;
    int     natgc, tlen;
    FILE    *fp;

    if ((fp = fopen(file, "r")) == 0) {
        fprintf(stderr, "%s: can't read %s\n", prog, file);
        exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
        if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
    }
    if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
        fprintf(stderr, "%s: malloc( ) failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
    pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

Table 1 (cont')

...getseq

```

py = pseq + 4;
*len = tlen;
rewind(fp);

while (fgets(line, 1024, fp)) {
    if (*line == ';' || *line == '<' || *line == '>')
        continue;
    for (px = line; *px != '\n'; px++) {
        if (isupper(*px))
            *py++ = *px;
        else if (islower(*px))
            *py++ = toupper(*px);
        if (index("ATGCU", *(py-1)))
            natgc++;
    }
    *py++ = '\0';
    *py = '\0';
    (void) fclose(fp);
    dna = natgc > (tlen/3);
    return(pseq+4);
}

char *
g_alloc(msg, nx, sz)
char *msg;          /* program, calling routine */
int nx, sz;          /* number and size of elements */
{
    char *px, *calloc( );

    if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
        if (*msg) {
            fprintf(stderr, "%s: g_alloc( ) failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
            exit(1);
        }
    }
    return(px);
}

/*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main( )
 */
readjmps( )
{
    int fd = -1;
    int siz, i0, i1;
    register i, j, xx;

    if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
            fprintf(stderr, "%s: can't open( ) %s\n", prog, jname);
            cleanup(1);
        }
    }

    for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
        while (1) {
            for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                ;

```

g\_alloc

readjmps

**Table 1 (cont')**

...readjumps

```

    if (j < 0 && dx[dmax].offset && fj) {
        (void) lseek(fd, dx[dmax].offset, 0);
        (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
        (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
        dx[dmax].ijmp = MAXJMP-1;
    }
    else
        break;
}
if (i >= JMPS) {
    fprintf(stderr, "%s: too many gaps in alignment\n", prog);
    cleanup(1);
}
if (j >= 0) {
    siz = dx[dmax].jp.n[j];
    xx = dx[dmax].jp.x[j];
    dmax += siz;
    if (siz < 0) { /* gap in second seq */
        pp[1].n[i1] = -siz;
        xx += siz;
        /* id = xx - yy + len1 - 1
        */
        pp[1].x[i1] = xx - dmax + len1 - 1;
        gapy++;
        ngapy -= siz;
        /* ignore MAXGAP when doing endgaps */
        siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
        i1++;
    }
    else if (siz > 0) { /* gap in first seq */
        pp[0].n[i0] = siz;
        pp[0].x[i0] = xx;
        gapx++;
        ngapx += siz;
        /* ignore MAXGAP when doing endgaps */
        siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
        i0++;
    }
}
else
    break;
}

/* reverse the order of jumps
*/
for (j = 0, i0--; j < i0; j++, i0--) {
    i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
    i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
}
for (j = 0, i1--; j < i1; j++, i1--) {
    i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
    i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
}
if (fd >= 0)
    (void) close(fd);
if (fj) {
    (void) unlink(jname);
    fj = 0;
    offset = 0;
}

```

**Table 1 (cont')**

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw( )
 */
writejumps(ix)                                     writejumps
{
    int      ix;
    char     *mktemp( );

    if (!fj) {
        if (mktemp(jname) < 0) {
            fprintf(stderr, "%s: can't mktemp( ) %s\n", prog, jname);
            cleanup(1);
        }
        if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
    }
    (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
    (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}

```

Table 2

PRO	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXXXXYYYYYY	(Length = 12 amino acids)

5      % amino acid sequence identity =  
 (the number of identically matching amino acid residues between the two polypeptide sequences as determined by  
 ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =  
 5 divided by 15 = 33.3%

Table 3

PRO	XXXXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXXXYYYYYYZZYZ	(Length = 15 amino acids)

10  
 15      % amino acid sequence identity =  
 (the number of identically matching amino acid residues between the two polypeptide sequences as determined by  
 ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =  
 5 divided by 10 = 50%

Table 4

20      PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLL	(Length = 16 nucleotides)

25      % nucleic acid sequence identity =  
 (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-  
 2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =  
 6 divided by 14 = 42.9%

Table 5

30      PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

35      % nucleic acid sequence identity =  
 (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-  
 2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =  
 4 divided by 12 = 33.3%

## 5.2. Compositions and Methods of the Invention

### 5.2.1. PRO Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO polypeptide such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO polypeptide or in various domains of the PRO polypeptide described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO polypeptide that results in a change in the amino acid sequence of the PRO polypeptide as compared with the native sequence PRO polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, *i.e.*, conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.



Table 6

	Original Residue	Exemplary Substitutions	Preferred Substitutions
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
10	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe; norleucine	leu
15	Leu (L)	norleucine; ile; val; met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
20	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter *et al.*, Nucl. Acids Res., 13:4331 (1986); Zoller *et al.*, Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells *et al.*, Gene, 34:315 (1985)], restriction selection mutagenesis [Wells *et al.*, Philos. Trans. R. Soc. London SerA, 317:415

(1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

#### 5.2.2. Modifications of PRO Polypeptides

Covalent modifications of PRO polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking the PRO polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidyl)propionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparagyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the  $\alpha$ -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in the native sequence PRO polypeptide (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO polypeptide (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino

acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, *e.g.*, in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, *et al.*, Arch. Biochem. Biophys., 259:52 (1987) and by Edge *et al.*, Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura *et al.*, Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of the PRO polypeptide comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, *e.g.*, polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO polypeptide of the present invention may also be modified in a way to form a chimeric molecule comprising the PRO polypeptide fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO polypeptide with a protein transduction domain which targets the PRO polypeptide for delivery to various tissues and more particularly across the brain blood barrier, using, for example, the protein transduction domain of human immunodeficiency virus TAT protein (Schwarze *et al.*, 1999, *Science* 285: 1569-72).

In another embodiment, such a chimeric molecule comprises a fusion of the PRO polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO polypeptide. The presence of such epitope-tagged forms of the PRO polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-His) or poly-histidine-glycine (poly-His-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field *et al.*, Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan *et al.*, Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky *et al.*, Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp *et al.*, BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin *et al.*, *Science*, 255:192-194 (1992)]; an  $\alpha$ -tubulin epitope peptide [Skinner *et al.*, J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth *et al.*, Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions

preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions *see* also, U.S. Patent No. 5,428,130 issued June 27, 1995.

5                   5.2.3.   Preparation of the PRO Polypeptide

          The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given  
10   DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the PRO DNA as well as all further native homologues and variants included in the foregoing definition of PRO polypeptides, will be referred to as "PRO" regardless of their origin or mode of preparation.

          The description below relates primarily to production of PRO polypeptides by culturing cells transformed or transfected with a vector containing nucleic acid encoding PRO polypeptides. It is, of course, contemplated that alternative methods that are well known in the art may be employed to prepare the PRO polypeptide. For instance, the PRO polypeptide sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques. *See, e.g.,* Stewart *et al.*, Solid-Phase Peptide Synthesis (W.H. Freeman Co.: San Francisco, CA, 1969); Merrifield, J. Am. Chem. Soc., **85**: 2149-2154 (1963). *In vitro* protein synthesis may be performed using manual  
15   techniques or by automation. Automated synthesis may be accomplished, for instance, with an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO polypeptide.

                  5.2.3.1. Isolation of DNA Encoding PRO Polypeptides

25           DNA encoding the PRO polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the mRNA encoding the PRO polypeptide and to express it at a detectable level. Accordingly, DNAs encoding the human PRO polypeptide can be conveniently obtained from cDNA libraries prepared from human tissues, such as described in the Examples. The gene encoding the PRO polypeptide may also be obtained from a genomic library or by oligonucleotide synthesis.

30           Libraries can be screened with probes (such as antibodies to the PRO polypeptide or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook *et al.*, *supra*. An alternative means to isolate the gene encoding the PRO polypeptide is to use PCR methodology. Sambrook *et al.*, *supra*; Dieffenbach *et al.*, PCR Primer: A Laboratory Manual (New York: Cold

Spring Harbor Laboratory Press, 1995).

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like  $^{32}\text{P}$ -labeled ATP, biotinylation, or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook *et al.*, *supra*.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined through sequence alignment using computer software programs such as ALIGN, DNASTar, and INHERIT, which employ various algorithms to measure homology.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook *et al.*, *supra*, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

#### 5.2.3.2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH, and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: A Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook *et al.*, *supra*.

Methods of transfection are known to the ordinarily skilled artisan, for example,  $\text{CaPO}_4$  treatment and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook *et al.*, *supra*, or electroporation is generally used for prokaryotes or other cells that contain substantial cell-wall barriers. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw *et al.*, Gene, **23**: 315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, **52**:456-457 (1978) can be employed. General aspects of mammalian cell host system transformations have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen *et al.*, J. Bact., **130**: 946 (1977) and Hsiao *et al.*, Proc. Natl. Acad. Sci. (USA), **76**: 3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, *e.g.*, polybrene or polyornithine, may also be used. For various techniques for

transforming mammalian cells, *see*, Keown *et al.*, Methods in Enzymology, 185: 527-537 (1990) and Mansour *et al.*, Nature, 336: 348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include, but are not limited to, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325); and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, *e.g.*, *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, *e.g.*, *Salmonella typhimurium*, *Serratia*, *e.g.*, *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (*e.g.*, *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, *e.g.*, PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for vectors encoding the PRO polypeptide. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer *et al.*, Bio/Technology, 9: 968-975 (1991)) such as, *e.g.*, *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt *et al.*, J. Bacteriol., 737 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg *et al.*, Bio/Technology, 8: 135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna *et al.*, J. Basic Microbiol., 28: 265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case *et al.*, Proc. Natl. Acad. Sci. USA, 76: 5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, *e.g.*, *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance *et al.*, Biochem. Biophys. Res. Commun., 112: 284-289 [1983]; Tilburn *et al.*, Gene, 26: 205-221 [1983]; Yelton *et al.*, Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4: 475-479 [1985]). Methylophilic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*,

*Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylootrophs, 269 (1982).

Suitable host cells for the expression of nucleic acid encoding glycosylated PRO polypeptides are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham *et al.*, J. Gen. Virol., 36: 59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

#### 5.2.3.3. Selection and Use of a Replicable Vector

The nucleic acid (*e.g.*, cDNA or genomic DNA) encoding the PRO polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence if the sequence is to be secreted, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques that are known to the skilled artisan.

The PRO polypeptide may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the DNA encoding the PRO polypeptide that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, *e.g.*, the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces*  $\alpha$ -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 $\mu$  plasmid origin

is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV, or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, *e.g.*, the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the nucleic acid encoding the PRO polypeptide such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7. Stinchcomb *et al.*, Nature, 282: 39 (1979); Kingsman *et al.*, Gene, 7: 141 (1979); Tschemper *et al.*, Gene, 10: 157 (1980). The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1. Jones, Genetics, 85: 12 (1977).

Expression and cloning vectors usually contain a promoter operably linked to the nucleic acid sequence encoding the PRO polypeptide to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the  $\beta$ -lactamase and lactose promoter systems (Chang *et al.*, Nature, 275: 615 (1978); Goeddel *et al.*, Nature, 281: 544 (1979)), alkaline phosphatase, a tryptophan (*trp*) promoter system (Goeddel, Nucleic Acids Res., 8: 4057 (1980); EP 36,776), and hybrid promoters such as the *tac* promoter (deBoer *et al.*, Proc. Natl. Acad. Sci. USA, 80: 21-25 (1983)). Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding the PRO polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase (Hitzeman *et al.*, J. Biol. Chem., 255: 2073 (1980)) or other glycolytic enzymes (Hess *et al.*, J. Adv. Enzyme Reg., 7: 149 (1968); Holland, Biochemistry, 17: 4900 (1978)), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters that are inducible promoters having the additional advantage of transcription controlled by growth conditions are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO nucleic acid transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus, and Simian Virus 40 (SV40); by heterologous mammalian promoters, *e.g.*, the actin



promoter or an immunoglobulin promoter; and by heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin,  $\alpha$ -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the sequence coding for PRO polypeptides, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding the PRO polypeptide.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of the PRO polypeptide in recombinant vertebrate cell culture are described in Gething *et al.*, Nature, 293: 620-625 (1981); Mantei *et al.*, Nature, 281: 40-46 (1979); EP 117,060; and EP 117,058.

#### 5.2.3.4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native-sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to DNA encoding the PRO polypeptide and encoding a specific antibody epitope.

#### 5.2.3.5. Purification of PRO Polypeptides

Forms of PRO polypeptides may be recovered from culture medium or from host cell lysates. If

membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g., TRITON-X™ 100) or by enzymatic cleavage. Cells employed in expression of nucleic acid encoding the PRO polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell-lysing agents. It may be desired to purify the PRO polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described, for example, in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice (Springer-Verlag: New York, 1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO polypeptide produced.

#### 5.2.4. Uses of PRO Polypeptides

##### 5.2.4.1. Assays for Cardiovascular, Endothelial, and Angiogenic Activity

Various assays can be used to test the polypeptide herein for cardiovascular, endothelial, and angiogenic activity. Such assays include those provided in the Examples below.

Assays for testing for endothelin antagonist activity, as disclosed in U.S. Pat. No. 5,773,414, include a rat heart ventricle binding assay where the polypeptide is tested for its ability to inhibit iodinated endothelin-1 binding in a receptor assay, an endothelin receptor binding assay testing for intact cell binding of radiolabeled endothelin-1 using rabbit renal artery vascular smooth muscle cells, an inositol phosphate accumulation assay where functional activity is determined in Rat-1 cells by measuring intra-cellular levels of second messengers, an arachidonic acid release assay that measures the ability of added compounds to reduce endothelin-stimulated arachidonic acid release in cultured vascular smooth muscles, *in vitro* (isolated vessel) studies using endothelium from male New Zealand rabbits, and *in vivo* studies using male Sprague-Dawley rats.

Assays for tissue generation activity include, without limitation, those described in WO 95/16035 (bone, cartilage, tendon); WO 95/05846 (nerve, neuronal), and WO 91/07491 (skin, endothelium).

Assays for wound-healing activity include, for example, those described in Winter, Epidermal Wound Healing, Maibach, HI and Rovee, DT, eds. (Year Book Medical Publishers, Inc., Chicago), pp. 71-112, as modified by the article of Eaglstein and Mertz, J. Invest. Dermatol., 71: 382-384 (1978).

An assay to screen for a test molecule relating to a PRO polypeptide that binds an endothelin B<sub>1</sub> (ETB<sub>1</sub>) receptor polypeptide and modulates signal transduction activity involves providing a host cell transformed with a DNA encoding endothelin B<sub>1</sub> receptor polypeptide, exposing the cells to the test candidate, and measuring endothelin B<sub>1</sub> receptor signal transduction activity, as described, e.g., in U.S. Pat. No. 5,773,223.

There are several cardiac hypertrophy assays. *In vitro* assays include induction of spreading of adult rat cardiac myocytes. In this assay, ventricular myocytes are isolated from a single (male Sprague-Dawley) rat,

essentially following a modification of the procedure described in detail by Piper *et al.*, "Adult ventricular rat heart muscle cells" in Cell Culture Techniques in Heart and Vessel Research, H.M. Piper, ed. (Berlin: Springer-Verlag, 1990), pp. 36-60. This procedure permits the isolation of adult ventricular myocytes and the long-term culture of these cells in the rod-shaped phenotype. Phenylephrine and Prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) have been shown to induce a spreading response in these adult cells. The inhibition of myocyte spreading induced by PGF<sub>2α</sub> or PGF<sub>2α</sub> analogs (e.g., fluprostenol) and phenylephrine by various potential inhibitors of cardiac hypertrophy is then tested.

One example of an *in vivo* assay is a test for inhibiting cardiac hypertrophy induced by fluprostenol *in vivo*. This pharmacological model tests the ability of the PRO polypeptide to inhibit cardiac hypertrophy induced in rats (e.g., male Wistar or Sprague-Dawley) by subcutaneous injection of fluprostenol (an agonist analog of PGF<sub>2α</sub>). It is known that rats with pathologic cardiac hypertrophy induced by myocardial infarction have chronically elevated levels of extractable PGF<sub>2α</sub> in their myocardium. Lai *et al.*, Am. J. Physiol. (Heart Circ. Physiol.), 271: H2197-H2208 (1996). Accordingly, factors that can inhibit the effects of fluprostenol on myocardial growth *in vivo* are potentially useful for treating cardiac hypertrophy. The effects of the PRO polypeptide on cardiac hypertrophy are determined by measuring the weight of heart, ventricles, and left ventricle (normalized by body weight) relative to fluprostenol-treated rats not receiving the PRO polypeptide.

Another example of an *in vivo* assay is the pressure-overload cardiac hypertrophy assay. For *in vivo* testing it is common to induce pressure-overload cardiac hypertrophy by constriction of the abdominal aorta of test animals. In a typical protocol, rats (e.g., male Wistar or Sprague-Dawley) are treated under anesthesia, and the abdominal aorta of each rat is narrowed down just below the diaphragm. Beznak M., Can. J. Biochem. Physiol., 33: 985-94 (1955). The aorta is exposed through a surgical incision, and a blunted needle is placed next to the vessel. The aorta is constricted with a ligature of silk thread around the needle, which is immediately removed and which reduces the lumen of the aorta to the diameter of the needle. This approach is described, for example, in Rossi *et al.*, Am. Heart J., 124: 700-709 (1992) and O'Rourke and Reibel, P.S.E.M.B., 200: 95-100 (1992).

In yet another *in vivo* assay, the effect on cardiac hypertrophy following experimentally induced myocardial infarction (MI) is measured. Acute MI is induced in rats by left coronary artery ligation and confirmed by electrocardiographic examination. A sham-operated group of animals is also prepared as control animals. Earlier data have shown that cardiac hypertrophy is present in the group of animals with MI, as evidenced by an 18% increase in heart weight-to-body weight ratio. Lai *et al.*, *supra*. Treatment of these animals with candidate blockers of cardiac hypertrophy, e.g., the PRO polypeptide, provides valuable information about the therapeutic potential of the candidates tested. One further such assay test for induction of cardiac hypertrophy is disclosed in U.S. Pat. No. 5,773,415, using Sprague-Dawley rats.

For cancer, a variety of well-known animal models can be used to further understand the role of the genes identified herein in the development and pathogenesis of tumors, and to test the efficacy of candidate therapeutic agents, including antibodies and other antagonists of native PRO polypeptides, such as small-molecule antagonists. The *in vivo* nature of such models makes them particularly predictive of responses in human patients. Animal models of tumors and cancers (e.g., breast cancer, colon cancer, prostate cancer, lung cancer, etc.) include both non-recombinant and recombinant (transgenic) animals. Non-recombinant animal models include, for example,

rodent, *e.g.*, murine models. Such models can be generated by introducing tumor cells into syngeneic mice using standard techniques, *e.g.*, subcutaneous injection, tail vein injection, spleen implantation, intraperitoneal implantation, implantation under the renal capsule, or orthotopic implantation, *e.g.*, colon cancer cells implanted in colonic tissue. *See, e.g.*, PCT publication No. WO 97/33551, published September 18, 1997. Probably the most often used animal species in oncological studies are immunodeficient mice and, in particular, nude mice. The observation that the nude mouse with thymic hypo/aplasia could successfully act as a host for human tumor xenografts has led to its widespread use for this purpose. The autosomal recessive *nu* gene has been introduced into a very large number of distinct congenic strains of nude mouse, including, for example, ASW, A/He, AKR, BALB/c, B10.LP, C17, C3H, C57BL, C57, CBA, DBA, DDD, I/st, NC, NFR, NFS, NFS/N, NZB, NZC, NZW, P, RIII, and SJL. In addition, a wide variety of other animals with inherited immunological defects other than the nude mouse have been bred and used as recipients of tumor xenografts. For further details *see, e.g.*, The Nude Mouse in Oncology Research, E. Boven and B. Winograd, eds. (CRC Press, Inc., 1991).

The cells introduced into such animals can be derived from known tumor/cancer cell lines, such as any of the above-listed tumor cell lines, and, for example, the B104-1-1 cell line (stable NIH-3T3 cell line transfected with the *neu* protooncogene); *ras*-transfected NIH-3T3 cells; Caco-2 (ATCC HTB-37); or a moderately well-differentiated grade II human colon adenocarcinoma cell line, HT-29 (ATCC HTB-38); or from tumors and cancers. Samples of tumor or cancer cells can be obtained from patients undergoing surgery, using standard conditions involving freezing and storing in liquid nitrogen. Karmali *et al.*, Br. J. Cancer, 48: 689-696 (1983).

Tumor cells can be introduced into animals such as nude mice by a variety of procedures. The subcutaneous (s.c.) space in mice is very suitable for tumor implantation. Tumors can be transplanted s.c. as solid blocks, as needle biopsies by use of a trocar, or as cell suspensions. For solid-block or trocar implantation, tumor tissue fragments of suitable size are introduced into the s.c. space. Cell suspensions are freshly prepared from primary tumors or stable tumor cell lines, and injected subcutaneously. Tumor cells can also be injected as subdermal implants. In this location, the inoculum is deposited between the lower part of the dermal connective tissue and the s.c. tissue.

Animal models of breast cancer can be generated, for example, by implanting rat neuroblastoma cells (from which the *neu* oncogene was initially isolated), or *neu*-transformed NIH-3T3 cells into nude mice, essentially as described by Drebin *et al.* Proc. Nat. Acad. Sci. USA, 83: 9129-9133 (1986).

Similarly, animal models of colon cancer can be generated by passaging colon cancer cells in animals, *e.g.*, nude mice, leading to the appearance of tumors in these animals. An orthotopic transplant model of human colon cancer in nude mice has been described, for example, by Wang *et al.*, Cancer Research, 54: 4726-4728 (1994) and Too *et al.*, Cancer Research, 55: 681-684 (1995). This model is based on the so-called "METAMOUSE™" sold by AntiCancer, Inc., (San Diego, California).

Tumors that arise in animals can be removed and cultured *in vitro*. Cells from the *in vitro* cultures can then be passaged to animals. Such tumors can serve as targets for further testing or drug screening. Alternatively, the tumors resulting from the passage can be isolated and RNA from pre-passage cells and cells isolated after one or more rounds of passage analyzed for differential expression of genes of interest. Such passaging techniques can

be performed with any known tumor or cancer cell lines.

For example, Meth A, CMS4, CMS5, CMS21, and WEHI-164 are chemically induced fibrosarcomas of BALB/c female mice (DeLeo *et al.*, J. Exp. Med., **146**: 720 (1977)), which provide a highly controllable model system for studying the anti-tumor activities of various agents. Palladino *et al.*, J. Immunol., **138**: 4023-4032 (1987). Briefly, tumor cells are propagated *in vitro* in cell culture. Prior to injection into the animals, the cell lines are washed and suspended in buffer, at a cell density of about  $10 \times 10^6$  to  $10 \times 10^7$  cells/ml. The animals are then infected subcutaneously with 10 to 100  $\mu$ l of the cell suspension, allowing one to three weeks for a tumor to appear.

In addition, the Lewis lung (3LL) carcinoma of mice, which is one of the most thoroughly studied experimental tumors, can be used as an investigational tumor model. Efficacy in this tumor model has been correlated with beneficial effects in the treatment of human patients diagnosed with small-cell carcinoma of the lung (SCCL). This tumor can be introduced in normal mice upon injection of tumor fragments from an affected mouse or of cells maintained in culture. Zupi *et al.*, Br. J. Cancer, **41**: suppl. 4, 30 (1980). Evidence indicates that tumors can be started from injection of even a single cell and that a very high proportion of infected tumor cells survive. For further information about this tumor model *see*, Zacharski, Haemostasis, **16**: 300-320 (1986).

One way of evaluating the efficacy of a test compound in an animal model with an implanted tumor is to measure the size of the tumor before and after treatment. Traditionally, the size of implanted tumors has been measured with a slide caliper in two or three dimensions. The measure limited to two dimensions does not accurately reflect the size of the tumor; therefore, it is usually converted into the corresponding volume by using a mathematical formula. However, the measurement of tumor size is very inaccurate. The therapeutic effects of a drug candidate can be better described as treatment-induced growth delay and specific growth delay. Another important variable in the description of tumor growth is the tumor volume doubling time. Computer programs for the calculation and description of tumor growth are also available, such as the program reported by Rygaard and Spang-Thomsen, Proc. 6th Int. Workshop on Immune-Deficient Animals, Wu and Sheng eds. (Basel, 1989), p. 301. It is noted, however, that necrosis and inflammatory responses following treatment may actually result in an increase in tumor size, at least initially. Therefore, these changes need to be carefully monitored, by a combination of a morphometric method and flow cytometric analysis.

Further, recombinant (transgenic) animal models can be engineered by introducing the coding portion of the PRO gene identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 6148-615 (1985)); gene targeting in embryonic stem cells (Thompson *et al.*, Cell, **56**: 313-321 (1989)); electroporation of embryos (Lo, Mol. Cell. Biol., **3**: 1803-1814 (1983)); and sperm-mediated gene transfer. Lavitrano *et al.*, Cell, **57**: 717-73 (1989). For a review, *see* for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in

concatamers, *e.g.*, head-to-head or head-to-tail tandems. Selective introduction of a transgene into a particular cell type is also possible by following, for example, the technique of Lasko *et al.*, Proc. Natl. Acad. Sci. USA, **89**: 6232-636 (1992). The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ* hybridization, Northern blot analysis, PCR, or immunocytochemistry. The animals are further examined for signs of tumor or cancer development.

Alternatively, "knock-out" animals can be constructed that have a defective or altered gene encoding a PRO polypeptide identified herein, as a result of homologous recombination between the endogenous gene encoding the PRO polypeptide and altered genomic DNA encoding the same polypeptide introduced into an embryonic cell of the animal. For example, cDNA encoding a particular PRO polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular PRO polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker that can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector. *See, e.g.*, Thomas and Capecchi, Cell, **51**: 503 (1987) for a description of homologous recombination vectors. The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected. *See, e.g.*, Li *et al.*, Cell, **69**: 915 (1992). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse or rat) to form aggregation chimeras. *See, e.g.*, Bradley, in Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, E. J. Robertson, ed. (IRL: Oxford, 1987), pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock-out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized, for instance, by their ability to defend against certain pathological conditions and by their development of pathological conditions due to absence of the PRO polypeptide.

The efficacy of antibodies specifically binding the PRO polypeptides identified herein, and other drug candidates, can be tested also in the treatment of spontaneous animal tumors. A suitable target for such studies is the feline oral squamous cell carcinoma (SCC). Feline oral SCC is a highly invasive, malignant tumor that is the most common oral malignancy of cats, accounting for over 60% of the oral tumors reported in this species. It rarely metastasizes to distant sites, although this low incidence of metastasis may merely be a reflection of the short survival times for cats with this tumor. These tumors are usually not amenable to surgery, primarily because of the anatomy of the feline oral cavity. At present, there is no effective treatment for this tumor. Prior to entry into the study, each cat undergoes complete clinical examination and biopsy, and is scanned by computed tomography (CT). Cats diagnosed with sublingual oral squamous cell tumors are excluded from the study. The tongue can become paralyzed as a result of such tumor, and even if the treatment kills the tumor, the animals may not be able to feed themselves. Each cat is treated repeatedly, over a longer period of time. Photographs of the tumors will be taken daily during the treatment period, and at each subsequent recheck. After treatment, each cat undergoes another CT

scan. CT scans and thoracic radiograms are evaluated every 8 weeks thereafter. The data are evaluated for differences in survival, response, and toxicity as compared to control groups. Positive response may require evidence of tumor regression, preferably with improvement of quality of life and/or increased life span.

In addition, other spontaneous animal tumors, such as fibrosarcoma, adenocarcinoma, lymphoma, chondroma, or leiomyosarcoma of dogs, cats, and baboons can also be tested. Of these, mammary adenocarcinoma in dogs and cats is a preferred model as its appearance and behavior are very similar to those in humans. However, the use of this model is limited by the rare occurrence of this type of tumor in animals.

Other *in vitro* and *in vivo* cardiovascular, endothelial, and angiogenic tests known in the art are also suitable herein.

#### 5.2.4.2. Tissue Distribution

The results of the cardiovascular, endothelial, and angiogenic assays herein can be verified by further studies, such as by determining mRNA expression in various human tissues.

As noted before, gene amplification and/or gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native-sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for *in situ* hybridization are provided hereinbelow.

#### 5.2.4.3. Antibody Binding Studies

The results of the cardiovascular, endothelial, and angiogenic study can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides on endothelial cells or other cells used in the cardiovascular, endothelial, and angiogenic assays is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies, the preparation of which will be described hereinbelow.

Antibody binding studies may be carried out in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, Monoclonal Antibodies: A Manual of Techniques (CRC Press, Inc., 1987), pp.147-158.

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies preferably are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte that remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody that is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. *See, e.g.*, U.S. Pat. No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

#### 5.2.4.4. Cell-Based Tumor Assays

Cell-based assays and animal models for cardiovascular, endothelial, and angiogenic disorders, such as tumors, can be used to verify the findings of a cardiovascular, endothelial, and angiogenic assay herein, and further to understand the relationship between the genes identified herein and the development and pathogenesis of undesirable cardiovascular, endothelial, and angiogenic cell growth. The role of gene products identified herein in the development and pathology of undesirable cardiovascular, endothelial, and angiogenic cell growth, *e.g.*, tumor cells, can be tested by using cells or cells lines that have been identified as being stimulated or inhibited by the PRO polypeptide herein. Such cells include, for example, those set forth in the Examples below.

In a different approach, cells of a cell type known to be involved in a particular cardiovascular, endothelial, and angiogenic disorder are transfected with the cDNAs herein, and the ability of these cDNAs to induce excessive growth or inhibit growth is analyzed. If the cardiovascular, endothelial, and angiogenic disorder is cancer, suitable tumor cells include, for example, stable tumor cell lines such as the B104-1-1 cell line (stable NIH-3T3 cell line transfected with the *neu* protooncogene) and *ras*-transfected NIH-3T3 cells, which can be transfected with the desired gene and monitored for tumorigenic growth. Such transfected cell lines can then be used to test the ability of poly- or monoclonal antibodies or antibody compositions to inhibit tumorigenic cell growth by exerting cytostatic or cytotoxic activity on the growth of the transformed cells, or by mediating antibody-dependent cellular cytotoxicity (ADCC). Cells transfected with the coding sequences of the genes identified herein can further be used to identify drug candidates for the treatment of cardiovascular, endothelial, and angiogenic disorders such as cancer.

In addition, primary cultures derived from tumors in transgenic animals (as described above) can be used in the cell-based assays herein, although stable cell lines are preferred. Techniques to derive continuous cell lines from transgenic animals are well known in the art. *See, e.g.*, Small *et al.*, Mol. Cell. Biol., 5: 642-648 (1985).



#### 5.2.4.5. Gene Therapy

Described below are methods and compositions whereby disease symptoms may be ameliorated. Certain diseases are brought about, at least in part, by an excessive level of gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of such disease symptoms.

Alternatively, certain other diseases are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a gene product's activity. As such, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease symptoms.

In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a target gene's expression, or the activity of the target gene product, will reinforce the protective effect it exerts. Some disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease symptoms.

The PRO polypeptides described herein and polypeptidyl agonists and antagonists may be employed in accordance with the present invention by expression of such polypeptides *in vivo*, which is often referred to as gene therapy.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells: *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the sites where the PRO polypeptide is required, *i.e.*, the site of synthesis of the PRO polypeptide, if known, and the site (*e.g.*, wound) where biological activity of the PRO polypeptide is needed. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells, and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes that are implanted into the patient (*see, e.g.*, U.S. Pat. Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or transferred *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, transduction, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. Transduction involves the association of a replication-defective, recombinant viral (preferably retroviral) particle with a cellular receptor, followed by introduction of the nucleic acids contained by the particle into the cell. A commonly used vector for *ex vivo* delivery of the gene is a retrovirus.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral or non-viral vectors (such as adenovirus, lentivirus, Herpes simplex I virus, or adeno-associated virus (AAV)) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are, for example, DOTMA, DOPE, and DC-Chol; *see, e.g.*, Tonkinson *et al.*, Cancer Investigation, 14(1): 54-65 (1996)). The most preferred vectors for use in gene therapy are viruses, most preferably adenoviruses, AAV, lentiviruses, or retroviruses. A viral vector such as a retroviral vector includes at least one transcriptional promoter/enhancer or locus-defining element(s), or other

elements that control gene expression by other means such as alternate splicing, nuclear RNA export, or post-translational modification of messenger. In addition, a viral vector such as a retroviral vector includes a nucleic acid molecule that, when transcribed in the presence of a gene encoding the PRO polypeptide, is operably linked thereto and acts as a translation initiation sequence. Such vector constructs also include a packaging signal, long terminal repeats (LTRs) or portions thereof, and positive and negative strand primer binding sites appropriate to the virus used (if these are not already present in the viral vector). In addition, such vector typically includes a signal sequence for secretion of the PRO polypeptide from a host cell in which it is placed. Preferably the signal sequence for this purpose is a mammalian signal sequence, most preferably the native signal sequence for the PRO polypeptide. Optionally, the vector construct may also include a signal that directs polyadenylation, as well as one or more restriction sites and a translation termination sequence. By way of example, such vectors will typically include a 5' LTR, a tRNA binding site, a packaging signal, an origin of second-strand DNA synthesis, and a 3' LTR or a portion thereof. Other vectors can be used that are non-viral, such as cationic lipids, polylysine, and dendrimers.

In some situations, it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell-surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins that bind to a cell-surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, *e.g.*, capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins that undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem., **262**: 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA, **87**: 3410-3414 (1990). For a review of the currently known gene marking and gene therapy protocols, see, Anderson *et al.*, Science, **256**: 808-813 (1992). See also WO 93/25673 and the references cited therein.

Suitable gene therapy and methods for making retroviral particles and structural proteins can be found in, *e.g.*, U.S. Pat. No. 5,681,746.

#### 5.2.4.6. Use of Gene as a Diagnostic

This invention is also related to the use of the gene encoding the PRO polypeptide as a diagnostic. Detection of a mutated form of the PRO polypeptide will allow a diagnosis of a cardiovascular, endothelial, and angiogenic disease or a susceptibility to a cardiovascular, endothelial, and angiogenic disease, such as a tumor, since mutations in the PRO polypeptide may cause tumors.

Individuals carrying mutations in the genes encoding a human PRO polypeptide may be detected at the DNA level by a variety of techniques. Nucleic acids for diagnosis may be obtained from a patient's cells, such as from blood, urine, saliva, tissue biopsy, and autopsy material. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR (Saiki *et al.*, Nature, **324**: 163-166 (1986)) prior to analysis. RNA or cDNA may also be used for the same purpose. As an example, PCR primers complementary to the nucleic acid encoding the PRO polypeptide can be used to identify and analyze the PRO polypeptide mutations. For example, deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal

genotype. Point mutations can be identified by hybridizing amplified DNA to radiolabeled RNA encoding the PRO polypeptide, or alternatively, radiolabeled antisense DNA sequences encoding the PRO polypeptide. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase A digestion or by differences in melting temperatures.

5 Genetic testing based on DNA sequence differences may be achieved by detection of alteration in electrophoretic mobility of DNA fragments in gels with or without denaturing agents. Small sequence deletions and insertions can be visualized by high resolution gel electrophoresis. DNA fragments of different sequences may be distinguished on denaturing formamide gradient gels in which the mobilities of different DNA fragments are retarded in the gel at different positions according to their specific melting or partial melting temperatures. See, 10 *e.g.*, Myers *et al.*, Science, 230: 1242 (1985).

Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method, for example, Cotton *et al.*, Proc. Natl. Acad. Sci. USA, 85: 4397-4401 (1985).

15 Thus, the detection of a specific DNA sequence may be achieved by methods such as hybridization, RNase protection, chemical cleavage, direct DNA sequencing, or the use of restriction enzymes, *e.g.*, restriction fragment length polymorphisms (RFLP), and Southern blotting of genomic DNA.

#### 5.2.4.7. Use to Detect PRO Polypeptide Levels

In addition to more conventional gel-electrophoresis and DNA sequencing, mutations can also be detected by *in situ* analysis.

20 Expression of nucleic acid encoding the PRO polypeptide may be linked to vascular disease or neovascularization associated with tumor formation. If the PRO polypeptide has a signal sequence and the mRNA is highly expressed in endothelial cells and to a lesser extent in smooth muscle cells, this indicates that the PRO polypeptide is present in serum. Accordingly, an anti-PRO polypeptide antibody could be used to diagnose vascular disease or neovascularization associated with tumor formation, since an altered level of this PRO polypeptide may 25 be indicative of such disorders.

A competition assay may be employed wherein antibodies specific to the PRO polypeptide are attached to a solid support and the labeled PRO polypeptide and a sample derived from the host are passed over the solid support and the amount of label detected attached to the solid support can be correlated to a quantity of the PRO polypeptide in the sample.

#### 30 5.2.4.8. Chromosome Mapping

The sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphisms) are presently available for marking chromosomal 35 location. The mapping of DNAs to chromosomes according to the present invention is an important first step in

correlating those sequences with genes associated with disease.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis for the 3'- untranslated region is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular DNA to a particular chromosome. Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include *in situ* hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome-specific cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 500 or 600 bases; however, clones larger than 2,000 bp have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. FISH requires use of the clones from which the gene encoding the PRO polypeptide was derived, and the longer the better. For example, 2,000 bp is good, 4,000 bp is better, and more than 4,000 is probably not necessary to get good results a reasonable percentage of the time. For a review of this technique, see, Verma *et al.*, Human Chromosomes: a Manual of Basic Techniques (Pergamon Press, New York, 1988).

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available online through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region is then identified through linkage analysis (coinheritance of physically adjacent genes).

Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease.

With current resolution of physical mapping and genetic mapping techniques, a cDNA precisely localized to a chromosomal region associated with the disease could be one of between 50 and 500 potential causative genes. (This assumes 1 megabase mapping resolution and one gene per 20 kb).

#### 5.2.4.9. Screening Assays for Drug Candidates

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptide encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other

cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

5 All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

10 In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

20 If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, *e.g.*, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340: 245-246 (1989); Chien *et al.*, Proc. Natl. Acad. Sci. USA, 88: 9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for  $\beta$ -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

If the PRO polypeptide has the ability to stimulate the proliferation of endothelial cells in the presence of the co-mitogen ConA, then one example of a screening method takes advantage of this ability. Specifically, in the proliferation assay, human umbilical vein endothelial cells are obtained and cultured in 96-well flat-bottomed culture plates (Costar, Cambridge, MA) and supplemented with a reaction mixture appropriate for facilitating proliferation of the cells, the mixture containing Con-A (Calbiochem, La Jolla, CA). Con-A and the compound to be screened are added and after incubation at 37°C, cultures are pulsed with <sup>3</sup>H-thymidine and harvested onto glass fiber filters (pH; Cambridge Technology, Watertown, MA). Mean <sup>3</sup>H-thymidine incorporation (cpm) of triplicate cultures is determined using a liquid scintillation counter (Beckman Instruments, Irvine, CA). Significant <sup>3</sup>(H)-thymidine incorporation indicates stimulation of endothelial cell proliferation.

To assay for antagonists, the assay described above is performed; however, in this assay the PRO polypeptide is added along with the compound to be screened and the ability of the compound to inhibit <sup>3</sup>(H)thymidine incorporation in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan *et al.*, Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to the labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is

resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

5 In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with the labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

10 The compositions useful in the treatment of cardiovascular, endothelial, and angiogenic disorders include, without limitation, antibodies, small organic and inorganic molecules, peptides, phosphopeptides, antisense and ribozyme molecules, triple-helix molecules, etc., that inhibit the expression and/or activity of the target gene product.

15 More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with a PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

20 Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, *e.g.*, an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - *see*, Lee *et al.*, Nucl. Acids Res., 6:3073 (1979); Cooney *et al.*, Science, 241: 456 (1988); Dervan *et al.*, Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; 25 in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex helix formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988).

The antisense oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger, *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre, *et al.*, 1987, *Proc. Natl. Acad. Sci. U.S.A.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *BioTechniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an  $\alpha$ -anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier, *et al.*, 1987, *Nucl. Acids Res.* 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue, *et al.*, 1987, *Nucl. Acids Res.* 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue, *et al.*, 1987, *FEBS Lett.* 215:327-330).

Oligonucleotides of the invention may be synthesized by standard methods known in the art, *e.g.*, by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein, *et al.* (1988, *Nucl. Acids Res.* 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin, *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:7448-7451), etc.



The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, *e.g.*, between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

5 Antisense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 15 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 35 bases in length, about 40 bases in length, about 45 bases in length, about 50 bases in length, about 55 bases in length, about 60 bases in length, about 65 bases in length, about 70 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 90 bases in length, about 95 bases in length, about 100 bases in length,  
10 or more.

Potential antagonists further include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

15 Additional potential antagonists are ribozymes, which are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details *see, e.g.*, Rossi, Current Biology, 4: 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

20 While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy target gene mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions which form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Myers, 1995, *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers, New York, (see especially Figure 4, page  
25 833) and in Haseloff and Gerlach, 1988, *Nature*, 334:585-591, which is incorporated herein by reference in its entirety.

30 Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target gene mRNA, *i.e.*, to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Thomas Cech and collaborators (Zaug, *et al.*, 1984, *Science*, 224:574-578; Zaug and Cech, 1986, *Science*, 231:470-475; Zaug, *et al.*, 1986, *Nature*, 324:429-433; published  
35 International patent application No. WO 88/04300 by University Patents Inc.; Been and Cech, 1986, *Cell*, 47:207-216). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence

whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that are present in the target gene.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (*e.g.*, for improved stability, targeting, *etc.*) and should be delivered to cells that express the target gene *in vivo*. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous target gene messages and inhibit translation. Because ribozymes, unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details *see, e.g.*, PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

#### 5.2.4.10. Types of Cardiovascular, Endothelial, and Angiogenic Disorders to be Treated

The PRO polypeptides, or agonists or antagonists thereto, that have activity in the cardiovascular, angiogenic, and endothelial assays described herein, and/or whose gene product has been found to be localized to the cardiovascular system, are likely to have therapeutic uses in a variety of cardiovascular, endothelial, and angiogenic disorders, including systemic disorders that affect vessels, such as diabetes mellitus. Their therapeutic utility could include diseases of the arteries, capillaries, veins, and/or lymphatics. Examples of treatments hereunder include treating muscle wasting disease, treating osteoporosis, aiding in implant fixation to stimulate the growth of cells around the implant and therefore facilitate its attachment to its intended site, increasing IGF stability in tissues or in serum, if applicable, and increasing binding to the IGF receptor (since IGF has been shown *in vitro* to enhance human marrow erythroid and granulocytic progenitor cell growth).

The PRO polypeptides or agonists or antagonists thereto may also be employed to stimulate erythropoiesis or granulopoiesis, to stimulate wound healing or tissue regeneration and associated therapies concerned with re-growth of tissue, such as connective tissue, skin, bone, cartilage, muscle, lung, or kidney, to promote angiogenesis, to stimulate or inhibit migration of endothelial cells, and to proliferate the growth of vascular smooth muscle and endothelial cell production. The increase in angiogenesis mediated by the PRO polypeptide or agonist would be beneficial to ischemic tissues and to collateral coronary development in the heart subsequent to coronary stenosis. Antagonists are used to inhibit the action of such polypeptides, for example, to limit the production of excess connective tissue during wound healing or pulmonary fibrosis if the PRO polypeptide promotes such production. This would include treatment of acute myocardial infarction and heart failure.

Moreover, the present invention provides the treatment of cardiac hypertrophy, regardless of the underlying cause, by administering a therapeutically effective dose of the PRO polypeptide, or agonist or antagonist thereto. If the objective is the treatment of human patients, the PRO polypeptide preferably is recombinant human PRO

polypeptide (rhPRO polypeptide). The treatment for cardiac hypertrophy can be performed at any of its various stages, which may result from a variety of diverse pathologic conditions, including myocardial infarction, hypertension, hypertrophic cardiomyopathy, and valvular regurgitation. The treatment extends to all stages of the progression of cardiac hypertrophy, with or without structural damage of the heart muscle, regardless of the underlying cardiac disorder.

The decision of whether to use the molecule itself or an agonist thereof for any particular indication, as opposed to an antagonist to the molecule, would depend mainly on whether the molecule herein promotes cardiovascularization, genesis of endothelial cells, or angiogenesis or inhibits these conditions. For example, if the molecule promotes angiogenesis, an antagonist thereof would be useful for treatment of disorders where it is desired to limit or prevent angiogenesis. Examples of such disorders include vascular tumors such as haemangioma, tumor angiogenesis, neovascularization in the retina, choroid, or cornea, associated with diabetic retinopathy or premature infant retinopathy or macular degeneration and proliferative vitreoretinopathy, rheumatoid arthritis, Crohn's disease, atherosclerosis, ovarian hyperstimulation, psoriasis, endometriosis associated with neovascularization, restenosis subsequent to balloon angioplasty, scar tissue overproduction, for example, that seen in a keloid that forms after surgery, fibrosis after myocardial infarction, or fibrotic lesions associated with pulmonary fibrosis.

If, however, the molecule inhibits angiogenesis, it would be expected to be used directly for treatment of the above conditions.

On the other hand, if the molecule stimulates angiogenesis it would be used itself (or an agonist thereof) for indications where angiogenesis is desired such as peripheral vascular disease, hypertension, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, arterial restenosis, thrombophlebitis, lymphangitis, lymphedema, wound healing and tissue repair, ischemia reperfusion injury, angina, myocardial infarctions such as acute myocardial infarctions, chronic heart conditions, heart failure such as congestive heart failure, and osteoporosis.

If, however, the molecule inhibits angiogenesis, an antagonist thereof would be used for treatment of those conditions where angiogenesis is desired.

Specific types of diseases are described below, where the PRO polypeptide herein or agonists or antagonists thereof may serve as useful for vascular-related drug targeting or as therapeutic targets for the treatment or prevention of the disorders. Atherosclerosis is a disease characterized by accumulation of plaques of intimal thickening in arteries, due to accumulation of lipids, proliferation of smooth muscle cells, and formation of fibrous tissue within the arterial wall. The disease can affect large, medium, and small arteries in any organ. Changes in endothelial and vascular smooth muscle cell function are known to play an important role in modulating the accumulation and regression of these plaques.

Hypertension is characterized by raised vascular pressure in the systemic arterial, pulmonary arterial, or portal venous systems. Elevated pressure may result from or result in impaired endothelial function and/or vascular disease.

Inflammatory vasculitides include giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa (including the microangiopathic form), Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, and a variety

of infectious-related vascular disorders (including Henoch-Schonlein purpura). Altered endothelial cell function has been shown to be important in these diseases.

Reynaud's disease and Reynaud's phenomenon are characterized by intermittent abnormal impairment of the circulation through the extremities on exposure to cold. Altered endothelial cell function has been shown to be important in this disease.

Aneurysms are saccular or fusiform dilatations of the arterial or venous tree that are associated with altered endothelial cell and/or vascular smooth muscle cells.

Arterial restenosis (restenosis of the arterial wall) may occur following angioplasty as a result of alteration in the function and proliferation of endothelial and vascular smooth muscle cells.

Thrombophlebitis and lymphangitis are inflammatory disorders of veins and lymphatics, respectively, that may result from, and/or in, altered endothelial cell function. Similarly, lymphedema is a condition involving impaired lymphatic vessels resulting from endothelial cell function.

The family of benign and malignant vascular tumors are characterized by abnormal proliferation and growth of cellular elements of the vascular system. For example, lymphangiomas are benign tumors of the lymphatic system that are congenital, often cystic, malformations of the lymphatics that usually occur in newborns. Cystic tumors tend to grow into the adjacent tissue. Cystic tumors usually occur in the cervical and axillary region. They can also occur in the soft tissue of the extremities. The main symptoms are dilated, sometimes reticular, structured lymphatics and lymphocysts surrounded by connective tissue. Lymphangiomas are assumed to be caused by improperly connected embryonic lymphatics or their deficiency. The result is impaired local lymph drainage. Griener *et al.*, *Lymphology*, 4: 140-144 (1971).

Another use for the PRO polypeptides herein or agonists or antagonists thereto is in the prevention of tumor angiogenesis, which involves vascularization of a tumor to enable it to grow and/or metastasize. This process is dependent on the growth of new blood vessels. Examples of neoplasms and related conditions that involve tumor angiogenesis include breast carcinomas, lung carcinomas, gastric carcinomas, esophageal carcinomas, colorectal carcinomas, liver carcinomas, ovarian carcinomas, thecomas, arrhenoblastomas, cervical carcinomas, endometrial carcinoma, endometrial hyperplasia, endometriosis, fibrosarcomas, choriocarcinoma, head and neck cancer, nasopharyngeal carcinoma, laryngeal carcinomas, hepatoblastoma, Kaposi's sarcoma, melanoma, skin carcinomas, hemangioma, cavernous hemangioma, hemangioblastoma, pancreas carcinomas, retinoblastoma, astrocytoma, glioblastoma, Schwannoma, oligodendroglioma, medulloblastoma, neuroblastomas, rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcomas, urinary tract carcinomas, thyroid carcinomas, Wilm's tumor, renal cell carcinoma, prostate carcinoma, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome.

Age-related macular degeneration (AMD) is a leading cause of severe visual loss in the elderly population. The exudative form of AMD is characterized by choroidal neovascularization and retinal pigment epithelial cell detachment. Because choroidal neovascularization is associated with a dramatic worsening in prognosis, the PRO polypeptide or agonist or antagonist thereto is expected to be useful in reducing the severity of AMD.

Healing of trauma such as wound healing and tissue repair is also a targeted use for the PRO polypeptides herein or their agonists or antagonists. Formation and regression of new blood vessels is essential for tissue healing and repair. This category includes bone, cartilage, tendon, ligament, and/or nerve tissue growth or regeneration, as well as wound healing and tissue repair and replacement, and in the treatment of burns, incisions, and ulcers.

5 A PRO polypeptide or agonist or antagonist thereof that induces cartilage and/or bone growth in circumstances where bone is not normally formed has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a PRO polypeptide or agonist or antagonist thereof may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma-

10 induced, or oncologic, resection-induced craniofacial defects, and also is useful in cosmetic plastic surgery.

PRO polypeptides or agonists or antagonists thereto may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a PRO polypeptide or agonist or antagonist thereto may also exhibit activity for

15 generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, or endothelium), muscle (smooth, skeletal, or cardiac), and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate.

A PRO polypeptide herein or agonist or antagonist thereto may also be useful for gut protection or

20 regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage. Also, the PRO polypeptide or agonist or antagonist thereto may be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells, or for inhibiting the growth of tissues described above.

A PRO polypeptide or agonist or antagonist thereto may also be used in the treatment of periodontal

25 diseases and in other tooth-repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells, or induce differentiation of progenitors of bone-forming cells. A PRO polypeptide herein or an agonist or an antagonist thereto may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes, since blood

30 vessels play an important role in the regulation of bone turnover and growth.

Another category of tissue regeneration activity that may be attributable to the PRO polypeptide herein or agonist or antagonist thereto is tendon/ligament formation. A protein that induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed has application in the healing of tendon or ligament tears, deformities, and other tendon or ligament defects in humans and other animals. Such

35 a preparation may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the PRO polypeptide herein or

agonist or antagonist thereto contributes to the repair of congenital, trauma-induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions herein may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions herein may also be useful in the treatment of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The PRO polypeptide or its agonist or antagonist may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.*, for the treatment of central and peripheral nervous system disease and neuropathies, as well as mechanical and traumatic disorders, that involve degeneration, death, or trauma to neural cells or nerve tissue. More specifically, a PRO polypeptide or its agonist or antagonist may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions that may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma, and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a PRO polypeptide herein or agonist or antagonist thereto.

Ischemia-reperfusion injury is another indication. Endothelial cell dysfunction may be important in both the initiation of, and in regulation of the sequelae of events that occur following ischemia-reperfusion injury.

Rheumatoid arthritis is a further indication. Blood vessel growth and targeting of inflammatory cells through the vasculature is an important component in the pathogenesis of rheumatoid and sero-negative forms of arthritis.

A PRO polypeptide or its agonist or antagonist may also be administered prophylactically to patients with cardiac hypertrophy, to prevent the progression of the condition, and avoid sudden death, including death of asymptomatic patients. Such preventative therapy is particularly warranted in the case of patients diagnosed with massive left ventricular cardiac hypertrophy (a maximal wall thickness of 35 mm or more in adults, or a comparable value in children), or in instances when the hemodynamic burden on the heart is particularly strong.

A PRO polypeptide or its agonist or antagonist may also be useful in the management of atrial fibrillation, which develops in a substantial portion of patients diagnosed with hypertrophic cardiomyopathy.

Further indications include angina, myocardial infarctions such as acute myocardial infarctions, and heart failure such as congestive heart failure. Additional non-neoplastic conditions include psoriasis, diabetic and other proliferative retinopathies including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, nephrotic syndrome, preeclampsia, ascites, pericardial effusion (such as that associated with pericarditis), and pleural effusion.

In view of the above, the PRO polypeptides or agonists or antagonists thereof described herein, which are shown to alter or impact endothelial cell function, proliferation, and/or form, are likely to play an important role in the etiology and pathogenesis of many or all of the disorders noted above, and as such can serve as therapeutic targets to augment or inhibit these processes or for vascular-related drug targeting in these disorders.

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#### 5.2.4.11. Administration Protocols, Schedules, Doses, and Formulations

The molecules herein and agonists and antagonists thereto are pharmaceutically useful as a prophylactic and therapeutic agent for various disorders and diseases as set forth above.

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Therapeutic compositions of the PRO polypeptides or agonists or antagonists are prepared for storage by mixing the desired molecule having the appropriate degree of purity with optional pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences, 16th edition, Osol, A. ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN<sup>TM</sup>, PLURONICS<sup>TM</sup> or polyethylene glycol (PEG).

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Additional examples of such carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts, or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, and polyethylene glycol. Carriers for topical or gel-based forms of agonist or antagonist include polysaccharides such as sodium carboxymethylcellulose or methylcellulose, polyvinylpyrrolidone, polyacrylates, polyoxyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wood wax alcohols. For all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules, liposomes, plasters, inhalation forms, nose sprays, sublingual tablets, and sustained-release preparations. The PRO polypeptides or agonists or antagonists will typically be formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

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Another formulation comprises incorporating a PRO polypeptide or agonist or antagonist thereof into formed articles. Such articles can be used in modulating endothelial cell growth and angiogenesis. In addition, tumor invasion and metastasis may be modulated with these articles.

PRO polypeptides or agonists or antagonists to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution. PRO polypeptides ordinarily will be stored in lyophilized form or in solution if administered systemically. If in lyophilized form, the PRO polypeptide or agonist or antagonist thereto is typically formulated in combination with other ingredients for reconstitution with an appropriate diluent at the time for use. An example of a liquid formulation of a PRO polypeptide or agonist or antagonist is a sterile, clear, colorless unpreserved solution filled in a single-dose vial for subcutaneous injection. Preserved pharmaceutical compositions suitable for repeated use may contain, for example, depending mainly on the indication and type of polypeptide:

- a) PRO polypeptide or agonist or antagonist thereto;
- b) a buffer capable of maintaining the pH in a range of maximum stability of the polypeptide or other molecule in solution, preferably about 4-8;
- c) a detergent/surfactant primarily to stabilize the polypeptide or molecule against agitation-induced aggregation;
- d) an isotonicifier;
- e) a preservative selected from the group of phenol, benzyl alcohol and a benzethonium halide, *e.g.*, chloride; and
- f) water.

If the detergent employed is non-ionic, it may, for example, be polysorbates (*e.g.*, POLYSORBATE™ (TWEEN™) 20, 80, etc.) or poloxamers (*e.g.*, POLOXAMER™ 188). The use of non-ionic surfactants permits the formulation to be exposed to shear surface stresses without causing denaturation of the polypeptide. Further, such surfactant-containing formulations may be employed in aerosol devices such as those used in a pulmonary dosing, and needleless jet injector guns (*see, e.g.*, EP 257,956).

An isotonicifier may be present to ensure isotonicity of a liquid composition of the PRO polypeptide or agonist or antagonist thereto, and includes polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol, and mannitol. These sugar alcohols can be used alone or in combination. Alternatively, sodium chloride or other appropriate inorganic salts may be used to render the solutions isotonic.

The buffer may, for example, be an acetate, citrate, succinate, or phosphate buffer depending on the pH desired. The pH of one type of liquid formulation of this invention is buffered in the range of about 4 to 8, preferably about physiological pH.

The preservatives phenol, benzyl alcohol and benzethonium halides, *e.g.*, chloride, are known antimicrobial agents that may be employed.

Therapeutic PRO polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle. The formulations are preferably administered as repeated intravenous (*i.v.*), subcutaneous (*s.c.*), or intramuscular (*i.m.*) injections, or as aerosol formulations suitable for intranasal or intrapulmonary delivery (for intrapulmonary delivery *see, e.g.*, EP 257,956).



PRO polypeptides can also be administered in the form of sustained-released preparations. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the protein, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (*e.g.*, poly(2-hydroxyethyl-methacrylate) as described by Langer *et al.*, J. Biomed. Mater. Res., **15**: 167-277 (1981) and Langer, Chem. Tech., **12**: 98-105 (1982) or poly(vinylalcohol)), polylactides (U.S. Patent No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, Biopolymers, **22**: 547-556 (1983)), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), degradable lactic acid-glycolic acid copolymers such as the Lupron Depot™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated proteins remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for protein stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

Sustained-release PRO polypeptide compositions also include liposomally entrapped PRO polypeptides. Liposomes containing the PRO polypeptide are prepared by methods known *per se*: DE 3,218,121; Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688-3692 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese patent application 83-118008; U.S. Patent Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. % cholesterol, the selected proportion being adjusted for the optimal therapy.

The therapeutically effective dose of a PRO polypeptide or agonist or antagonist thereto will, of course, vary depending on such factors as the pathological condition to be treated (including prevention), the method of administration, the type of compound being used for treatment, any co-therapy involved, the patient's age, weight, general medical condition, medical history, etc., and its determination is well within the skill of a practicing physician. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the maximal therapeutic effect. If the PRO polypeptide has a narrow host range, for the treatment of human patients formulations comprising human PRO polypeptide, more preferably native-sequence human PRO polypeptide, are preferred. The clinician will administer the PRO polypeptide until a dosage is reached that achieves the desired effect for treatment of the condition in question. For example, if the objective is the treatment of CHF, the amount would be one that inhibits the progressive cardiac hypertrophy associated with this condition. The progress of this therapy is easily monitored by echo cardiography. Similarly, in patients with hypertrophic cardiomyopathy, the PRO polypeptide can be administered on an empirical basis.

With the above guidelines, the effective dose generally is within the range of from about 0.001 to about 1.0 mg/kg, more preferably about 0.01-1.0 mg/kg, most preferably about 0.01-0.1 mg/kg.

For non-oral use in treating human adult hypertension, it is advantageous to administer the PRO polypeptide in the form of an injection at about 0.01 to 50 mg, preferably about 0.05 to 20 mg, most preferably 1 to 20 mg, per kg body weight, 1 to 3 times daily by intravenous injection. For oral administration, a molecule based on the PRO polypeptide is preferably administered at about 5 mg to 1 g, preferably about 10 to 100 mg, per kg body weight, 1 to 3 times daily. It should be appreciated that endotoxin contamination should be kept minimally at a safe level, for example, less than 0.5 ng/mg protein. Moreover, for human administration, the formulations preferably meet sterility, pyrogenicity, general safety, and purity as required by FDA Office and Biologics standards.

The dosage regimen of a pharmaceutical composition containing the PRO polypeptide to be used in tissue regeneration will be determined by the attending physician considering various factors that modify the action of the polypeptides, *e.g.*, amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (*e.g.*, bone), the patient's age, sex, and diet, the severity of any infection, time of administration, and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF-I, to the final composition may also affect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations, and tetracycline labeling.

The route of PRO polypeptide or antagonist or agonist administration is in accord with known methods, *e.g.*, by injection or infusion by intravenous, intramuscular, intracerebral, intraperitoneal, intracerebrospinal, subcutaneous, intraocular, intraarticular, intrasynovial, intrathecal, oral, topical, or inhalation routes, or by sustained-release systems as noted below. The PRO polypeptide or agonist or antagonists thereof also are suitably administered by intratumoral, peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. The intraperitoneal route is expected to be particularly useful, for example, in the treatment of ovarian tumors.

If a peptide or small molecule is employed as an antagonist or agonist, it is preferably administered orally or non-orally in the form of a liquid or solid to mammals.

Examples of pharmacologically acceptable salts of molecules that form salts and are useful hereunder include alkali metal salts (*e.g.*, sodium salt, potassium salt), alkaline earth metal salts (*e.g.*, calcium salt, magnesium salt), ammonium salts, organic base salts (*e.g.*, pyridine salt, triethylamine salt), inorganic acid salts (*e.g.*, hydrochloride, sulfate, nitrate), and salts of organic acid (*e.g.*, acetate, oxalate, p-toluenesulfonate).

For compositions herein that are useful for bone, cartilage, tendon, or ligament regeneration, the therapeutic method includes administering the composition topically, systemically, or locally as an implant or device. When administered, the therapeutic composition for use is in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage, or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Preferably, for bone and/or cartilage formation, the composition would include a matrix capable of delivering the

protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and preferably capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance, and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid, and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above-mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

One specific embodiment is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the polypeptide compositions from disassociating from the matrix.

One suitable family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, one preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer, and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt%, based on total formulation weight, which represents the amount necessary to prevent desorption of the polypeptide (or its antagonist) from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the polypeptide (or its antagonist) the opportunity to assist the osteogenic activity of the progenitor cells.

#### 5.2.4.12. Combination Therapies

The effectiveness of the PRO polypeptide or an agonist or antagonist thereof in preventing or treating the disorder in question may be improved by administering the active agent serially or in combination with another agent that is effective for those purposes, either in the same composition or as separate compositions.

For example, for treatment of cardiac hypertrophy, PRO polypeptide therapy can be combined with the administration of inhibitors of known cardiac myocyte hypertrophy factors, e.g., inhibitors of  $\alpha$ -adrenergic agonists such as phenylephrine; endothelin-1 inhibitors such as BOSENTAN<sup>TM</sup> and MOXONODIN<sup>TM</sup>; inhibitors to CT-1

(U.S. Pat. No. 5,679,545); inhibitors to LIF; ACE inhibitors; des-aspartate-angiotensin I inhibitors (U.S. Pat. No. 5,773,415), and angiotensin II inhibitors.

For treatment of cardiac hypertrophy associated with hypertension, the PRO polypeptide can be administered in combination with  $\beta$ -adrenergic receptor blocking agents, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol; ACE inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, or nicardipine. Pharmaceutical compositions comprising the therapeutic agents identified herein by their generic names are commercially available, and are to be administered following the manufacturers' instructions for dosage, administration, adverse effects, contraindications, etc. *See, e.g., Physicians' Desk Reference* (Medical Economics Data Production Co.: Montvale, N.J., 1997), 51th Edition.

Preferred candidates for combination therapy in the treatment of hypertrophic cardiomyopathy are  $\beta$ -adrenergic-blocking drugs (*e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol), verapamil, diltiazem, or diltiazem. Treatment of hypertrophy associated with high blood pressure may require the use of antihypertensive drug therapy, using calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, or nicardipine;  $\beta$ -adrenergic blocking agents; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlorothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or ACE-inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril.

For other indications, PRO polypeptides or their agonists or antagonists may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as EGF, PDGF, TGF- $\alpha$  or TGF- $\beta$ , IGF, FGF, and CTGF.

In addition, PRO polypeptides or their agonists or antagonists used to treat cancer may be combined with cytotoxic, chemotherapeutic, or growth-inhibitory agents as identified above. Also, for cancer treatment, the PRO polypeptide or agonist or antagonist thereof is suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances.

The effective amounts of the therapeutic agents administered in combination with the PRO polypeptide or agonist or antagonist thereof will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve maximal management of the conditions to be treated. For example, for treating hypertension, these amounts ideally take into account use of diuretics or digitalis, and conditions such as hyper- or hypotension, renal impairment, etc. The dose will additionally depend on such factors as the type of the therapeutic agent to be used and the specific patient being treated. Typically, the amount employed will be the same dose as that used, if the given therapeutic agent is administered without the PRO polypeptide.

#### 5.2.4.13. Articles of Manufacture

An article of manufacture such as a kit containing the PRO polypeptide or agonists or antagonists thereof useful for the diagnosis or treatment of the disorders described above comprises at least a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition that is effective for diagnosing or treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the PRO polypeptide or an agonist or antagonist thereto. The label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use. The article of manufacture may also comprise a second or third container with another active agent as described above.

#### 5.2.5. Antibodies

Some of the most promising drug candidates according to the present invention are antibodies and antibody fragments that may inhibit the production or the gene product of the genes identified herein and/or reduce the activity of the gene products.

##### 5.2.5.1. Polyclonal Antibodies

Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include, but are not limited to, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants that may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A or synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

##### 5.2.5.2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal is typically immunized with an

immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. Goding, Monoclonal Antibodies: Principles and Practice (New York: Academic Press, 1986), pp. 59-103. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine, and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high-level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. Kozbor, J. Immunol., 133:3001 (1984); Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications (Marcel Dekker, Inc.: New York, 1987) pp. 51-63.

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the PRO polypeptide. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods. Goding, *supra*. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the

invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison *et al.*, *supra*) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy-chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

*In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

#### 5.2.5.3. Human and Humanized Antibodies

The anti-PRO antibodies may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub>, or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin, and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody preferably also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Jones *et al.*, Nature, **321**: 522-525 (1986); Riechmann *et al.*, Nature, **332**: 323-329 (1988); Presta, Curr. Op. Struct. Biol., **2**: 593-596 (1992).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones *et al.*, Nature, **321**: 522-525 (1986); Riechmann *et al.*, Nature, **332**: 323-327 (1988); Verhoeven *et al.*, Science, **239**: 1534-

1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381 (1991); Marks *et al.*, *J. Mol. Biol.*, 222: 581 (1991). The techniques of Cole *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies. Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985) and Boerner *et al.*, *J. Immunol.*, 147(1): 86-95 (1991). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed that closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016, and in the following scientific publications: Marks *et al.*, *Bio/Technology*, 10: 779-783 (1992); Lonberg *et al.*, *Nature*, 368: 856-859 (1994); Morrison, *Nature*, 368: 812-813 (1994); Fishwild *et al.*, *Nature Biotechnology*, 14: 845-851 (1996); Neuberger, *Nature Biotechnology*, 14: 826 (1996); Lonberg and Huszar, *Intern. Rev. Immunol.*, 13: 65-93 (1995).

#### 5.2.5.4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO polypeptide, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities. Milstein and Cuello, *Nature*, 305: 537-539 (1983). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, *EMBO J.*, 10: 3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant-domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further



details of generating bispecific antibodies, *see*, for example, Suresh *et al.*, Methods in Enzymology, **121**: 210 (1986).

#### 5.2.5.5. Heteroconjugate Antibodies

Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune-system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection. WO 91/00360; WO 92/200373; EP 03089. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide-exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

#### 5.2.5.6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). *See*, Caron *et al.*, J. Exp. Med., **176**: 1191-1195 (1992) and Shopes, J. Immunol., **148**: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.*, Cancer Research, **53**: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. *See*, Stevenson *et al.*, Anti-Cancer Drug Design, **3**: 219-230 (1989).

#### 5.2.5.7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include  $^{212}\text{Bi}$ ,  $^{131}\text{I}$ ,  $^{131}\text{In}$ ,  $^{90}\text{Y}$ , and  $^{186}\text{Re}$ .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives

of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See, WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such as streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is conjugated to a cytotoxic agent (e.g., a radionucleotide).

#### 5.2.5.8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See, Gabizon *et al.*, J. National Cancer Inst., 81(19): 1484 (1989).

#### 5.2.5.9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders as noted above and below in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and  $\gamma$  ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT<sup>TM</sup> (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

#### 5.2.5.10. Methods of Treatment using the Antibody

It is contemplated that the antibodies to a PRO polypeptide may be used to treat various cardiovascular, endothelial, and angiogenic conditions as noted above.

The antibodies are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous administration of the antibody is preferred.

Other therapeutic regimens may be combined with the administration of the antibodies of the instant invention as noted above. For example, if the antibodies are to treat cancer, the patient to be treated with such

antibodies may also receive radiation therapy. Alternatively, or in addition, a chemotherapeutic agent may be administered to the patient. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service, Ed., M.C. Perry (Williams & Wilkins: Baltimore, MD, 1992). The chemotherapeutic agent may precede, or follow administration of the antibody, or may be given simultaneously therewith. The antibody may be combined with an anti-estrogen compound such as tamoxifen or EVISTA<sup>TM</sup> or an anti-progesterone such as onapristone (*see*, EP 616812) in dosages known for such molecules.

If the antibodies are used for treating cancer, it may be desirable also to administer antibodies against other tumor-associated antigens, such as antibodies that bind to one or more of the ErbB2, EGFR, ErbB3, ErbB4, or VEGF receptor(s). These also include the agents set forth above. Also, the antibody is suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances. Alternatively, or in addition, two or more antibodies binding the same or two or more different antigens disclosed herein may be co-administered to the patient. Sometimes, it may be beneficial also to administer one or more cytokines to the patient. In a preferred embodiment, the antibodies herein are co-administered with a growth-inhibitory agent. For example, the growth-inhibitory agent may be administered first, followed by an antibody of the present invention. However, simultaneous administration or administration of the antibody of the present invention first is also contemplated. Suitable dosages for the growth-inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth-inhibitory agent and the antibody herein.

In one embodiment, vascularization of tumors is attacked in combination therapy. The anti-PRO polypeptide antibody and another antibody (*e.g.*, anti-VEGF) are administered to tumor-bearing patients at therapeutically effective doses as determined, for example, by observing necrosis of the tumor or its metastatic foci, if any. This therapy is continued until such time as no further beneficial effect is observed or clinical examination shows no trace of the tumor or any metastatic foci. Then TNF is administered, alone or in combination with an auxiliary agent such as alpha-, beta-, or gamma-interferon, anti-HER2 antibody, heregulin, anti-heregulin antibody, D-factor, interleukin-1 (IL-1), interleukin-2 (IL-2), granulocyte-macrophage colony stimulating factor (GM-CSF), or agents that promote microvascular coagulation in tumors, such as anti-protein C antibody, anti-protein S antibody, or C4b binding protein (*see*, WO 91/01753, published 21 February 1991), or heat or radiation.

Since the auxiliary agents will vary in their effectiveness, it is desirable to compare their impact on the tumor by matrix screening in conventional fashion. The administration of anti-PRO polypeptide antibody and TNF is repeated until the desired clinical effect is achieved. Alternatively, the anti-PRO polypeptide antibody is administered together with TNF and, optionally, auxiliary agent(s). In instances where solid tumors are found in the limbs or in other locations susceptible to isolation from the general circulation, the therapeutic agents described herein are administered to the isolated tumor or organ. In other embodiments, a FGF or PDGF antagonist, such as an anti-FGF or an anti-PDGF neutralizing antibody, is administered to the patient in conjunction with the anti-PRO

polypeptide antibody. Treatment with anti-PRO polypeptide antibodies preferably may be suspended during periods of wound healing or desirable neovascularization.

For the prevention or treatment of cardiovascular, endothelial, and angiogenic disorder, the appropriate dosage of an antibody herein will depend on the type of disorder to be treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments.

For example, depending on the type and severity of the disorder, about 1  $\mu\text{g/kg}$  to 50  $\text{mg/kg}$  (e.g., 0.1-20  $\text{mg/kg}$ ) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily or weekly dosage might range from about 1  $\mu\text{g/kg}$  to 100  $\text{mg/kg}$  or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated or sustained until a desired suppression of disorder symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays, including, for example, radiographic tumor imaging.

#### 5.2.5.11. Articles of Manufacture with Antibodies

An article of manufacture containing a container with the antibody and a label is also provided. Such articles are described above, wherein the active agent is an anti-PRO antibody.

#### 5.2.5.12. Diagnosis and Prognosis of Tumors using Antibodies

If the indication for which the antibodies are used is cancer, while cell-surface proteins, such as growth receptors over expressed in certain tumors, are excellent targets for drug candidates or tumor (e.g., cancer) treatment, the same proteins along with PRO polypeptides find additional use in the diagnosis and prognosis of tumors. For example, antibodies directed against the PRO polypeptides may be used as tumor diagnostics or prognostics.

For example, antibodies, including antibody fragments, can be used qualitatively or quantitatively to detect the expression of genes including the gene encoding the PRO polypeptide. The antibody preferably is equipped with a detectable, e.g., fluorescent label, and binding can be monitored by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. Such binding assays are performed essentially as described above.

*In situ* detection of antibody binding to the marker gene products can be performed, for example, by immunofluorescence or immunoelectron microscopy. For this purpose, a histological specimen is removed from the patient, and a labeled antibody is applied to it, preferably by overlaying the antibody on a biological sample. This procedure also allows for determining the distribution of the marker gene product in the tissue examined. It will be apparent to those skilled in the art that a wide variety of histological methods are readily available for *in situ* detection.

The following Examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

The disclosures of all patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

## 6. EXAMPLES

Commercially available reagents referred to in the Examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following Examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA. Unless otherwise noted, the present invention uses standard procedures of recombinant DNA technology, such as those described hereinabove and in the following textbooks: Sambrook *et al.*, supra; Ausubel *et al.*, Current Protocols in Molecular Biology (Green Publishing Associates and Wiley Interscience, N.Y., 1989); Innis *et al.*, PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc.: N.Y., 1990); Harlow *et al.*, Antibodies: A Laboratory Manual (Cold Spring Harbor Press: Cold Spring Harbor, 1988); Gait, Oligonucleotide Synthesis (IRL Press: Oxford, 1984); Freshney, Animal Cell Culture, 1987; Coligan *et al.*, Current Protocols in Immunology, 1991.

### 6.1. EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (*e.g.*, Dayhoff, GenBank), and proprietary databases (*e.g.* LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST-2 (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5 kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel *et al.*, Current Protocols in Molecular

Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; *see*, Holmes *et al.*, Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

## 6.2. EXAMPLE 2: Isolation of cDNA Clones by Amylase Screening

### 6.2.1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linked cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

### 6.2.2. Preparation of random primed cDNA library

A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linked with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

### 6.2.3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, *e.g.*, CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

5 The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL<sup>+</sup>, SUC<sup>+</sup>, GAL<sup>+</sup>. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec71*, *sec72*, *sec62*, with truncated *sec71* being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation  
10 of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz *et al.*, Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2  
15 x 10<sup>6</sup> cells/ml (approx. OD<sub>600</sub>=0.1) into fresh YEPD broth (500 ml) and regrown to 1 x 10<sup>7</sup> cells/ml (approx. OD<sub>600</sub>=0.4-0.5).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was  
20 discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li<sub>2</sub>OOCCH<sub>3</sub>), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 µl) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 µg, vol. < 10 µl) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 µl, 40% polyethylene glycol-4000,  
25 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li<sub>2</sub>OOCCH<sub>3</sub>, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 µl, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 µl) were spread onto the selective media previously prepared in 150 mm growth plates  
30 (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-  
35 210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely *et*



*al.*, *Anal. Biochem.*, **172**:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

#### 6.2.4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 µl) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 µl) was used as a template for the PCR reaction in a 25 µl volume containing: 0.5 µl KlenTaq (Clontech, Palo Alto, CA); 4.0 µl 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 µl Kentaq buffer (Clontech); 0.25 µl forward oligo 1; 0.25 µl reverse oligo 2; 12.5 µl distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAACGACGCGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:382)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:383)

PCR was then performed as follows:

a.	Denature	92°C, 5 minutes
b.	3 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	59°C, 30 seconds
	Extend	72°C, 60 seconds
c.	3 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	57°C, 30 seconds
	Extend	72°C, 60 seconds
d.	25 cycles of:	
	Denature	92°C, 30 seconds
	Anneal	55°C, 30 seconds
	Extend	72°C, 60 seconds
e.	Hold	4°C

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 µl) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook *et al.*, *supra*. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

### 6.3. EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc., (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

### 6.4. EXAMPLE 4: Isolation of cDNA clones Encoding Human PRO Polypeptides

Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were identified as encoding PRO polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Table 7

	<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
25	23330-1390	209775	4/14/1998
	23339-1130	209282	9/18/1997
	26846-1397	203406	10/27/1998
	26847-1395	209772	4/14/1998
	27865-1091	209296	9/23/1997
30	30868-1156	1437-PTA	3/2/2000
	30871-1157	209380	10/16/1997
	32286-1191	209385	10/16/1997
	33089-1132	209262	9/16/1997
	33092-1202	209420	10/28/1997

	33100-1159	209377	10/16/1997
	33223-1136	209264	9/16/1997
	34392-1170	209526	12/10/1997
	34431-1177	209399	10/17/1997
5	34433-1308	209719	3/31/1998
	34434-1139	209252	9/16/1997
	35600-1162	209370	10/16/1997
	35673-1201	209418	10/28/1997
	35880-1160	209379	10/16/1997
10	35918-1174	209402	10/17/1997
	36350-1158	209378	10/16/1997
	36638-1056	209456	11/12/1997
	38268-1188	209421	10/28/1997
	40370-1217	209485	11/21/1997
15	40628-1216	209432	11/7/1997
	43316-1237	209487	11/21/1997
	44196-1353	209847	5/6/1998
	45409-2511	203579	1/12/1999
	45419-1252	209616	2/5/1998
20	46777-1253	209619	2/5/1998
	48336-1309	209669	3/11/1998
	48606-1479	203040	7/1/1998
	49435-1219	209480	11/21/1997
	49631-1328	209806	4/28/1998
25	50919-1361	209848	5/6/1998
	50920-1325	209700	3/26/1998
	50921-1458	209859	5/12/1998
	52758-1399	209773	4/14/1998
	53517-1366-1	209802	4/23/1998
30	53915-1258	209593	1/21/1998
	53974-1401	209774	4/14/1998
	53987-1438	209858	5/12/1998
	56047-1456	209948	6/9/1998
	56050-1455	203011	6/23/1998
35	56110-1437	203113	8/11/1998
	56405-1357	209849	5/6/1998
	56433-1406	209857	5/12/1998

	56439-1376	209864	5/14/1998
	56529-1647	203293	9/29/1998
	56865-1491	203022	6/23/1998
	56965-1356	209842	5/6/1998
5	57033-1403-1	209905	5/27/1998
	57037-1444	209903	5/27/1998
	57039-1402	209777	4/14/1998
	57689-1385	209869	5/14/1998
	57690-1374	209950	6/9/1998
10	57694-1341	203017	6/23/1998
	57695-1340	203006	6/23/1998
	57699-1412	203020	6/23/1998
	57700-1408	203583	1/12/1999
	57708-1411	203021	6/23/1998
15	57838-1337	203014	6/23/1998
	58847-1383	209879	5/20/1998
	58852-1637	203271	9/22/1998
	58853-1423	203016	6/23/1998
	59212-1627	203245	9/9/1998
20	59220-1514	209962	6/9/1998
	59493-1420	203050	7/1/1998
	59497-1496	209941	6/4/1998
	59586-1520	203288	9/29/1998
	59588-1571	203106	8/11/1998
25	59620-1463	209989	6/16/1998
	59622-1334	209984	6/16/1998
	59777-1480	203111	8/11/1998
	59848-1512	203088	8/4/1998
	59849-1504	209986	6/16/1998
30	60621-1516	203091	8/4/1998
	60622-1525	203090	8/4/1998
	60764-1533	203452	11/10/1998
	60783-1611	203130	8/18/1998
	61755-1554	203112	8/11/1998
35	62306-1570	203254	9/9/1998
	62312-2558	203836	3/9/1999
	62814-1521	203093	8/4/1998

	62872-1509	203100	8/4/1998
	64883-1526	203253	9/9/1998
	64886-1601	203241	9/9/1998
	64889-1541	203250	9/9/1998
5	64896-1539	203238	9/9/1998
	64897-1628	203216	9/15/1998
	64903-1553	203223	9/15/1998
	64908-1163-1	203243	9/9/1998
	64950-1590	203224	9/15/1998
10	65402-1540	203252	9/9/1998
	65404-1551	203244	9/9/1998
	65405-1547	203476	11/17/1998
	65410-1569	203231	9/15/1998
	65412-1523	203094	8/4/1998
15	66307-2661	431-PTA	7/27/1999
	66526-1616	203246	9/9/1998
	66659-1593	203269	9/22/1998
	66660-1585	203279	9/22/1998
	66667-1596	203267	9/22/1998
20	66672-1586	203265	9/22/1998
	66675-1587	203282	9/22/1998
	67300-1605	203163	8/25/1998
	68818-2536	203657	2/9/1999
	68862-2546	203652	2/9/1999
25	68872-1620	203160	8/25/1998
	71290-1630	203275	9/22/1998
	73736-1657	203466	11/17/1998
	73739-1645	203270	9/22/1998
	73742-1662	203316	10/6/1998
30	76385-1692	203664	2/9/1999
	76393-1664	203323	10/6/1998
	76399-1700	203472	11/17/1998
	76400-2528	203573	1/12/1999
	76510-2504	203477	11/17/1998
35	76529-1666	203315	10/6/1998
	76532-1702	203473	11/17/1998
	76541-1675	203409	10/27/1998

	77503-1686	203362	10/20/1998
	77624-2515	203553	12/22/1998
	79230-2525	203549	12/22/1998
	79862-2522	203550	12/22/1998
5	80145-2594	204-PTA	6/8/1999
	80899-2501	203539	12/15/1998
	81754-2532	203542	12/15/1998
	81757-2512	203543	12/15/1998
	81761-2583	203862	3/23/1999
10	82358-2738	510-PTA	8/10/1999
	82364-2538	203603	1/20/1999
	82403-2959	2317-PTA	8/1/2000
	83500-2506	203391	10/29/1998
	83560-2569	203816	3/2/1999
15	84210-2576	203818	3/2/1999
	84920-2614	203966	4/27/1999
	86576-2595	203868	3/23/1999
	92218-2554	203834	3/9/1999
	92233-2599	134-PTA	5/25/1999
20	92256-2596	203891	3/30/1999
	92265-2669	256-PTA	6/22/1999
	92274-2617	203971	4/27/1999
	92929-2534-1	203586	1/12/1999
	93011-2637	20-PTA	5/4/1999
25	94854-2586	203864	3/23/1999
	96787-2534-1	203589	1/12/1999
	96867-2620	203972	4/27/1999
	96872-2674	550-PTA	8/17/1999
	96878-2626	23-PTA	5/4/1999
30	96889-2641	119-PTA	5/25/1999
	100312-2645	44-PTA	5/11/1999
	105782-2693	387-PTA	7/20/1999
	105849-2704	473-PTA	8/3/1999
	108725-2766	863-PTA	10/19/1999
35	108769-2765	861-PTA	10/19/1999
	119498-2965	2298-PTA	7/25/2000
	119535-2756	613-PTA	8/31/1999

	125185-2806	1031-PTA	12/7/1999
	131639-2874	1784-PTA	4/25/2000
	139623-2893	1670-PTA	4/11/2000
	143076-2787	1028-PTA	12/7/1999
5	143276-2975	2387-PTA	8/8/2000
	164625-2890	1535-PTA	3/21/2000
	167678-2963	2302-PTA	7/25/2000
	170021-2923	1906-PTA	5/23/2000
	170212-3000	2583-PTA	10/10/2000
10	177313-2982	2251-PTA	7/19/2000

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

6.5 EXAMPLE 5: Isolation of cDNA clones Encoding Human PRO1873, PRO7223, PRO7248, PRO730, PRO532, PRO7261, PRO734, PRO771, PRO2010, PRO5723, PRO3444, PRO9940, PRO3562, PRO10008, PRO5730, PRO6008, PRO4527, PRO4538 and PRO4553

DNA molecules encoding the PRO1873, PRO7223, PRO7248, PRO730, PRO532, PRO7261, PRO734, PRO771, PRO2010, PRO5723, PRO3444, PRO9940, PRO3562, PRO10008, PRO5730, PRO6008, PRO4527, PRO4538 and PRO4553 polypeptides shown in the accompanying figures were obtained through GenBank.

6.6. EXAMPLE 6: Use of PRO as a Hybridization Probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO (as shown in accompanying figures) or a fragment thereof is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

5 Hybridization and washing of filters containing either library DNAs is performed under the following high-stringency conditions. Hybridization of radiolabeled probe derived from the gene encoding PRO polypeptide to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

10 DNAs having a desired sequence identity with the DNA encoding full-length native sequence can then be identified using standard techniques known in the art.

#### 6.7. EXAMPLE 7: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

15 The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see, Bolivar *et al.*, Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a poly-His leader (including the first six STII codons, poly-His sequence, and enterokinase cleavage site),  
20 the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook *et al.*, *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA  
25 sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

30 After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences  
35 providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an



expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an OD<sub>600</sub> of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.71 g sodium citrate·2H<sub>2</sub>O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 ml water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO<sub>4</sub>) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

*E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni<sup>2+</sup>-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A<sub>280</sub> absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.8. EXAMPLE 8: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook *et al.*, *supra*. The resulting vector is called pRK5-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya *et al.*, *Cell*, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl<sub>2</sub>. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO<sub>4</sub>, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml <sup>35</sup>S-cysteine and 200 µCi/ml <sup>35</sup>S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of the PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompariyac *et al.*, *Proc. Natl. Acad. Sci.*, 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO<sub>4</sub> or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as <sup>35</sup>S-methionine. After determining the presence of a PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested.

The medium containing the expressed PRO polypeptide can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-His tag into a Baculovirus expression vector. The poly-His tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by  $\text{Ni}^{2+}$ -chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g., extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or as a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel *et al.*, Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used in expression in CHO cells is as described in Lucas *et al.*, Nucl. Acids Res., 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Qiagen), Dosper® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas *et al.*, *supra*. Approximately  $3 \times 10^7$  cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into a water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 ml of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 ml of selective media (0.2  $\mu\text{m}$  filtered PS20 with 5% 0.2  $\mu\text{m}$  diafiltered fetal bovine serum). The cells are then aliquoted into a 100 ml spinner containing 90 ml of selective media. After 1-2 days, the cells are transferred into a 250 ml spinner filled with 150 ml selective growth medium and incubated at 37°C. After another 2-3 days, 250 ml, 500 ml and 2000 ml spinners are seeded with  $3 \times 10^5$  cells/ml. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at  $1.2 \times 10^6$  cells/ml. On day 0, the cell number and pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 ml of 500 g/L

glucose and 0.6 ml of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability drops below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22  $\mu$ m filter. The filtrate is either stored at 4°C or immediately loaded onto columns for purification.

5 For the poly-His tagged constructs, the proteins are purified using a Ni<sup>2+</sup>-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni<sup>2+</sup>-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly  
10 purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before  
15 elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275  $\mu$ l of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### 20 6.9. EXAMPLE 9: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned  
25 into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by  
30 precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

35 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### 6.10. EXAMPLE 10: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO (such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley *et al.*, Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-His tagged PRO can then be purified, for example, by Ni<sup>2+</sup>-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert *et al.*, Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 ml Hepes, pH 7.9; 12.5 mM MgCl<sub>2</sub>; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni<sup>2+</sup>-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 ml, washed with 25 ml of water and equilibrated with 25 ml of loading buffer. The filtered cell extract is loaded onto the column at 0.5 ml per minute. The column is washed to baseline A<sub>280</sub> with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A<sub>280</sub> baseline again, the column is developed with a 0 to 500 mM imidazole gradient in the secondary wash buffer. One ml fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni<sup>2+</sup>-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His<sub>10</sub>-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Following PCR amplification, the respective coding sequences are subcloned into a baculovirus expression vector (pb.PH.IgG for IgG fusions and pb.PH.His.c for poly-His tagged proteins), and the vector and Baculogold® baculovirus DNA (Pharmingen) are co-transfected into 105 *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711), using Lipofectin (Gibco BRL). pb.PH.IgG and pb.PH.His are modifications of the commercially available baculovirus expression vector pVL1393 (Pharmingen), with modified polylinker regions to include the His or Fc tag sequences. The cells are grown in Hink's TNM-FH medium supplemented with 10% FBS (Hyclone). Cells are

incubated for 5 days at 28°C. The supernatant is harvested and subsequently used for the first viral amplification by infecting Sf9 cells in Hink's TNM-FH medium supplemented with 10% FBS at an approximate multiplicity of infection (MOI) of 10. Cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the constructs in the baculovirus expression vector is determined by batch binding of 1 ml of supernatant to 25 ml of Ni<sup>2+</sup>-NTA beads (QIAGEN) for histidine tagged proteins or Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The first viral amplification supernatant is used to infect a spinner culture (500 ml) of Sf9 cells grown in ESF-921 medium (Expression Systems LLC) at an approximate MOI of 0.1. Cells are incubated for 3 days at 28°C. The supernatant is harvested and filtered. Batch binding and SDS-PAGE analysis is repeated, as necessary, until expression of the spinner culture is confirmed.

The conditioned medium from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein construct is purified using a Ni<sup>2+</sup>-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni<sup>2+</sup>-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the proteins is verified by SDS polyacrylamide gel (PAGE) electrophoresis and N-terminal amino acid sequencing by Edman degradation.

Alternatively, a modified baculovirus procedure may be used incorporating high-5 cells. In this procedure, the DNA encoding the desired sequence is amplified with suitable systems, such as Pfu (Stratagene), or fused upstream (5'-of) of an epitope tag contained with a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pIE1-1 (Novagen). The pIE1-1 and pIE1-2 vectors are designed for constitutive expression of recombinant proteins from the baculovirus ie1 promoter in stably-transformed insect cells (1). The plasmids differ only in the orientation of the multiple cloning sites and contain all promoter sequences known to be important for ie1-mediated gene expression in uninfected insect cells as well as the hr5 enhancer element. pIE1-1 and pIE1-2 include the translation initiation site and can be used to produce fusion proteins. Briefly, the desired sequence or the desired portion of the sequence (such as the sequence encoding the

extracellular domain of a transmembrane protein) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector. For example, derivatives of pIE1-1 can include the Fc region of human IgG (pb.PH.IgG) or an 8 histidine (pb.PH.His) tag downstream (3'-of) the desired sequence. Preferably, the vector construct is sequenced for confirmation.

High-5 cells are grown to a confluency of 50% under the conditions of, 27°C, no CO<sub>2</sub>, NO pen/strep. For each 150 mm plate, 30 µg of pIE based vector containing the sequence is mixed with 1 ml Ex-Cell medium (Media: Ex-Cell 401 + 1/100 L-Glu JRH Biosciences #14401-78P (note: this media is light sensitive)), and in a separate tube, 100 µl of CellFectin (CellFECTIN (GibcoBRL #10362-010) (vortexed to mix)) is mixed with 1 ml of Ex-Cell medium. The two solutions are combined and allowed to incubate at room temperature for 15 minutes. 8 ml of Ex-Cell media is added to the 2 ml of DNA/CellFECTIN mix and this is layered on high-5 cells that have been washed once with Ex-Cell media. The plate is then incubated in darkness for 1 hour at room temperature. The DNA/CellFECTIN mix is then aspirated, and the cells are washed once with Ex-Cell to remove excess CellFECTIN, 30 ml of fresh Ex-Cell media is added and the cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the sequence in the baculovirus expression vector is determined by batch binding of 1 ml of supernatant to 25 ml of Ni<sup>2+</sup>-NTA beads (QIAGEN) for histidine tagged proteins or Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The conditioned media from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein comprising the sequence is purified using a Ni<sup>2+</sup>-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni<sup>2+</sup>-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 48°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is then subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the sequence is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation and other analytical procedures as desired or necessary.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### 6.11. EXAMPLE 11: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind the PRO polypeptide or an epitope on the PRO polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

5 Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

10 Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital  
15 bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then  
20 be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

25 The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

#### 6.12. EXAMPLE 12: Purification of PRO Polypeptides Using Specific Antibodies

30 Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

35 Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise,



monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

#### 6.13. EXAMPLE 13: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such

as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

#### 6.14. EXAMPLE 14: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

6.15. EXAMPLE 15: Stimulation of Endothelial Cell Proliferation (Assay 8)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to stimulate adrenal cortical capillary endothelial cell (ACE) growth. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus VEGF (5 ng/ml); and (4) ACE cells plus FGF (5ng/ml). The control or test sample, (in 100 microliter volumes), was then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were incubated for 6-7 days at 37°C/5% CO<sub>2</sub>. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter; 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of a PRO polypeptide was calculated as the fold increase in proliferation (as determined by the acid phosphatase activity, OD 405 nm) relative to (1) cell only background, and (2) relative to maximum stimulation by VEGF. VEGF (at 3-10 ng/ml) and FGF (at 1-5 ng/ml) were employed as an activity reference for maximum stimulation. Results of the assay were considered "positive" if the observed stimulation was  $\geq$  50% increase over background. VEGF (5 ng/ml) control at 1% dilution gave 1.24 fold stimulation; FGF (5 ng/ml) control at 1% dilution gave 1.46 fold stimulation.

PRO21 tested positive in this assay.

6.16. EXAMPLE 16: Inhibition of Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assay 9)

The ability of various PRO polypeptides to inhibit VEGF stimulated proliferation of endothelial cells was tested. Polypeptides testing positive in this assay are useful for inhibiting endothelial cell growth in mammals where such an effect would be beneficial, e.g., for inhibiting tumor growth.

Specifically, bovine adrenal cortical capillary endothelial cells (ACE) (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus 5 ng/ml FGF; (4) ACE cells plus 3 ng/ml VEGF; (5) ACE cells plus 3 ng/ml VEGF plus 1 ng/ml TGF-beta; and (6) ACE cells plus 3 ng/ml VEGF plus 5 ng/ml LIF. The test samples, poly-his tagged PRO polypeptides (in 100 microliter volumes), were then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were

incubated for 6-7 days at 37°C/5% CO<sub>2</sub>. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter; 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of PRO polypeptides was calculated as the percent inhibition of VEGF (3 ng/ml) stimulated proliferation (as determined by measuring acid phosphatase activity at OD 405 nm) relative to the cells without stimulation. TGF-beta was employed as an activity reference at 1 ng/ml, since TGF-beta blocks 70-90% of VEGF-stimulated ACE cell proliferation. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis. Numerical values (relative inhibition) are determined by calculating the percent inhibition of VEGF stimulated proliferation by the PRO polypeptides relative to cells without stimulation and then dividing that percentage into the percent inhibition obtained by TGF-β at 1 ng/ml which is known to block 70-90% of VEGF stimulated cell proliferation. The results are considered positive if the PRO polypeptide exhibits 30% or greater inhibition of VEGF stimulation of endothelial cell growth (relative inhibition 30% or greater).

PRO247, PRO720 and PRO4302 tested positive in this assay.

6.17. EXAMPLE 17: Enhancement of Heart Neonatal Hypertrophy Induced by LIF+ET-1 (Assay 75)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to enhance neonatal heart hypertrophy induced by LIF and endothelin-1 (ET-1). A test compound that provides a positive response in the present assay would be useful for the therapeutic treatment of cardiac insufficiency diseases or disorders characterized or associated with an undesired level of hypertrophy of the cardiac muscle.

Cardiac myocytes from 1-day old Harlan Sprague Dawley rats (180 μl at 7.5 x 10<sup>4</sup>/ml, serum <0.1, freshly isolated) are introduced on day 1 to 96-well plates previously coated with DMEM/F12 + 4%FCS. Test PRO polypeptide samples or growth medium alone (negative control) are then added directly to the wells on day 2 in 20 μl volume. LIF + ET-1 are then added to the wells on day 3. The cells are stained after an additional 2 days in culture and are then scored visually the next day. A positive in the assay occurs when the PRO polypeptide treated myocytes obtain a score greater than zero. A score of zero represents non-responsive cells whereas scores of 1 or 2 represent enhancement (*i.e.* they are visually larger on the average or more numerous than the untreated myocytes).

PRO21 polypeptides tested positive in this assay.

6.18. EXAMPLE 18: Detection of Endothelial Cell Apoptosis (FACS) (Assay 96)

The ability of PRO polypeptides of the present invention to induce apoptosis in endothelial cells was tested in human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in gelatinized T175 flasks using HUVEC cells below passage 10. PRO polypeptides testing positive in this assay are expected to be useful for

therapeutically treating conditions where apoptosis of endothelial cells would be beneficial including, for example, the therapeutic treatment of tumors.

On day one, the cells were split [420,000 cells per gelatinized 6 cm dishes - (11 x 10<sup>3</sup> cells/cm<sup>2</sup> Falcon, Primaria)] and grown in media containing serum (CS-C, Cell System) overnight or for 16 hours to 24 hours.

On day 2, the cells were washed 1x with 5 ml PBS ; 3 ml of 0% serum medium was added with VEGF (100 ng/ml); and 30 µl of the PRO test compound (final dilution 1%) or 0% serum medium (negative control) was added. The mixtures were incubated for 48 hours before harvesting.

The cells were then harvested for FACS analysis. The medium was aspirated and the cells washed once with PBS. 5 ml of 1 x trypsin was added to the cells in a T-175 flask, and the cells were allowed to stand until they were released from the plate (about 5-10 minutes). Trypsinization was stopped by adding 5 ml of growth media. The cells were spun at 1000 rpm for 5 minutes at 4°C. The media was aspirated and the cells were resuspended in 10 ml of 10% serum complemented medium (Cell Systems), 5 µl of Annexin-FITC (BioVison) added and chilled tubes were submitted for FACS. A positive result was determined to be enhanced apoptosis in the PRO polypeptide treated samples as compared to the negative control.

PRO4302 polypeptide tested positive in this assay.

#### 6.19. EXAMPLE 19: Induction of c-fos in HUVEC Cells (Assay 123)

This assay is designed to determine whether PRO polypeptides show the ability to induce c-fos in HUVEC cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in growth media (50% Ham's F12 w/o GHT: low glucose, and 50% DMEM without glycine: with NaHCO<sub>3</sub>, 1% glutamine, 10 mM HEPES, 10% FBS, 10 ng/ml bFGF) were plated on 96-well microtiter plates at a cell density of 5x10<sup>3</sup> cells/well. The day after plating (day 2), the cells were starved for 24 hours by removing the growth media and replacing with serum free media. On day 3, the cells are treated with 100 µl/well test samples and controls (positive control = growth media; negative control = Protein 32 buffer = 10 mM HEPES, 140 mM NaCl, 4% (w/v) mannitol, pH 6.8). One plate of cells was incubated for 30 minutes at 37°C, in 5% CO<sub>2</sub>. Another plate of cells was incubated for 60 minutes at 37°C, in 5% CO<sub>2</sub>. The samples were removed, and RNA was harvested using the RNeasy 96 kit (Qiagen). Next, the RNA was assayed for c-fos, egr-1 and GAPDH induction using Taqman.

The measure of activity of the fold increase over the negative control (Protein 32/HEPES buffer described above) value was by obtained by calculating the fold increase of the ratio of c-fos to GAPDH in test samples as compared to the negative control. The results are considered positive if the PRO polypeptide exhibits at least a two-fold value over the negative buffer control.

PRO1376 polypeptide tested positive in this assay.

6.20. EXAMPLE 20: Normal Human Iliac Artery Endothelial Cell Proliferation (Assay 138)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce proliferation of human iliac artery endothelial cells in culture and, therefore, function as useful growth factors.

On day 0, human iliac artery endothelial cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [epithelial cell growth media (EGM, Clonetics), plus supplements: human epithelial growth factor (hEGF), bovine brain extract (BBE), hydrocortisone, GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [EGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expressed as % of the cell growth observed with control buffer.

The following PRO polypeptides tested positive in this assay: PRO214, PRO238, PRO256, PRO363, PRO365, PRO791, PRO836, PRO1025, PRO1029, PRO1186, PRO1192, PRO1272, PRO1274, PRO1279, PRO1306, PRO1325, PRO1329, PRO1376, PRO1411, PRO1419, PRO1508, PRO1787, PRO1868, PRO1890, PRO4324, PRO4333, PRO4408, PRO4499, PRO5725, PRO6006, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21384 and PRO28631.

6.21. EXAMPLE 21: Pooled Human Umbilical Vein Endothelial Cell Proliferation (Assay 139)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce proliferation of pooled human umbilical vein endothelial cells in culture and, therefore, function as useful growth factors.

On day 0, pooled human umbilical vein endothelial cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [epithelial cell growth media (EGM, Clonetics), plus supplements: human epithelial growth factor (hEGF), bovine brain extract (BBE), hydrocortisone, GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [EGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expressed as % of the cell growth observed with control buffer.

The following PRO polypeptides tested positive in this assay: PRO181, PRO205, PRO221, PRO229, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO444, PRO533, PRO697, PRO725, PRO771, PRO788, PRO819, PRO827, PRO828, PRO846, PRO865, PRO1005, PRO1006, PRO1007, PRO1025, PRO1054, PRO1071, PRO1075, PRO1079, PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1184, PRO1190, PRO1192, PRO1195, PRO1244, PRO1272, PRO1273, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1412, PRO1419, PRO1474, PRO1477, PRO1488, PRO1550, PRO1556, PRO1760, PRO1782, PRO1787, PRO1801, PRO1868, PRO1887, PRO3438, PRO3444, PRO4302, PRO4324, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4405, PRO4422, PRO4425, PRO5723,

PRO5725, PRO5737, PRO5776, PRO6029, PRO6071, PRO7436, PRO9771, PRO10008, PRO10096, PRO21055 and PRO21384.

6.22. EXAMPLE 22: Human Coronary Artery Smooth Muscle Cell Proliferation (Assay 140)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce proliferation of human coronary artery smooth muscle cells in culture and, therefore, function as useful growth factors.

On day 0, human coronary artery smooth muscle cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [smooth muscle growth media (SmGM, Clonetics), plus supplements: insulin, human epithelial growth factor (hEGF), human fibroblast growth factor (hFGF), GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [SmGM plus 1 % FBS] and addition of PRO polypeptides at 1 %, 0.1 % and 0.01 %. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expressed as % of the cell growth observed with control buffer.

The following PRO polypeptides tested positive in this assay: PRO162, PRO181, PRO182, PRO195, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1080, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1265, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1309, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1488, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4302, PRO4333, PRO4345, PRO4353, PRO4354, PRO4405, PRO4408, PRO4430, PRO4503, PRO5725, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 and PRO21366.

6.23. EXAMPLE 23: Microarray Analysis to Detect Overexpression of PRO Polypeptides in HUVEC Cells Treated with Growth Factors

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce angiogenesis by stimulating endothelial cell tube formation in HUVEC cells.

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in tissues exposed to various stimuli (*e.g.*, growth factors) as compared to their normal, unexposed counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (exposed tissue) sample is greater than hybridization signal of a probe from a control (normal, unexposed tissue) sample, the gene or genes overexpressed in the exposed tissue are identified. The

implication of this result is that an overexpressed protein in an exposed tissue may be involved in the functional changes within the tissue following exposure to the stimuli (*e.g.*, tube formation).

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In the present example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in U.S. Provisional Patent Application Serial No. 60/193,767, filed on March 31, 2000 and which is herein incorporated by reference.

In the present example, HUVEC cells grown in either collagen gels or fibrin gels were induced to form tubes by the addition of various growth factors. Specifically, collagen gels were prepared as described previously in Yang *et al.*, *American J. Pathology*, 1999, 155(3):887-895 and Xin *et al.*, *American J. Pathology*, 2001, 158(3):1111-1120. Following gelation of the HUVEC cells, 1X basal medium containing M199 supplemented with 1%FBS, 1X ITS, 2 mM L-glutamine, 50 µg/ml ascorbic acid, 26.5 mM NaHCO<sub>3</sub>, 100U/ml penicillin and 100 U/ml streptomycin was added. Tube formation was elicited by the inclusion in the culture media of either a mixture of phorbol myrsitate acetate (50 nM), vascular endothelial cell growth factor (40 ng/ml) and basic fibroblast growth factor (40 ng/ml) ("PMA growth factor mix") or hepatocyte growth factor (40 ng/ml) and vascular endothelial cell growth factor (40 ng/ml) (HGF/VEGF mix) for the indicated period of time. Fibrin Gels were prepared by suspending Huvec (4 x 10<sup>5</sup> cells/ml) in M199 containing 1% fetal bovine serum (Hyclone) and human fibrinogen (2.5mg/ml). Thrombin (50U/ml) was then added to the fibrinogen suspension at a ratio of 1 part thrombin solution:30 parts fibrinogen suspension. The solution was then layered onto 10 cm tissue culture plates (total volume: 15 ml/plate) and allowed to solidify at 37°C for 20 min. Tissue culture media (10 ml of BM containing PMA (50 nM), bFGF (40ng/ml) and VEGF (40 ng/ml)) was then added and the cells incubated at 37°C in 5%CO<sub>2</sub> in air for the indicated period of time.

Total RNA was extracted from the HUVEC cells incubated for 0, 4, 8, 24, 40 and 50 hours in the different matrix and media combinations using a TRIzol extraction followed by a second purification using RNAeasy Mini Kit (Qiagen). The total RNA was used to prepare cRNA which was then hybridized to the microarrays.

In the present experiments, nucleic acid probes derived from the herein described PRO polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from the HUVEC cells described above were used for the hybridization thereto. Pairwise comparisons were made using time 0 chips as a baseline. Three replicate samples were analyzed for each experimental condition and time. Hence there were 3 time 0 samples for each treatment and 3 replicates of each successive time point. Therefore, a 3 by 3 comparison was performed for each time point compared against each time 0 point. This resulted in 9 comparisons per time point. Only those genes that had increased expression in all three non-time-0 replicates in each of the different matrix and media combinations as compared to any of the three time zero replicates were considered positive. Although this stringent method of data analysis does allow for false negatives, it minimizes false positives.

PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873,



PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 and PRO7261 tested positive in this assay.

#### 6.24. EXAMPLE 24: *In situ* Hybridization

*In situ* hybridization is a powerful and versatile technique for the detection and localization of nucleic acid sequences within cell or tissue preparations. It may be useful, for example, to identify sites of gene expression, analyze the tissue distribution of transcription, identify and localize viral infection, follow changes in specific mRNA synthesis, and aid in chromosome mapping.

*In situ* hybridization was performed following an optimized version of the protocol by Lu and Gillett, Cell Vision, 1: 169-176 (1994), using PCR-generated <sup>33</sup>P-labeled riboprobes. Briefly, formalin-fixed, paraffin-embedded human tissues were sectioned, deparaffinized, deproteinized in proteinase K (20 g/ml) for 15 minutes at 37°C, and further processed for *in situ* hybridization as described by Lu and Gillett, *supra*. A (<sup>33</sup>-P)UTP-labeled antisense riboprobe was generated from a PCR product and hybridized at 55°C overnight. The slides were dipped in Kodak NTB2<sup>TM</sup> nuclear track emulsion and exposed for 4 weeks.

##### 6.24.1. <sup>33</sup>P-Riboprobe synthesis

6.0 μl (125 mCi) of <sup>33</sup>P-UTP (Amersham BF 1002, SA < 2000 Ci/mmol) were speed-vacuum dried. To each tube containing dried <sup>33</sup>P-UTP, the following ingredients were added:

2.0 μl 5x transcription buffer

1.0 μl DTT (100 mM)

2.0 μl NTP mix (2.5 mM: 10 μl each of 10 mM GTP, CTP & ATP + 10 μl H<sub>2</sub>O)

1.0 μl UTP (50 μM)

1.0 μl RNAsin

1.0 μl DNA template (1 μg)

1.0 μl H<sub>2</sub>O

1.0 μl RNA polymerase (for PCR products T3 = AS, T7 = S, usually)

The tubes were incubated at 37°C for one hour. A total of 1.0 μl RQ1 DNase was added, followed by incubation at 37°C for 15 minutes. A total of 90 μl TE (10 mM Tris pH 7.6/1 mM EDTA pH 8.0) was added, and the mixture was pipetted onto DE81 paper. The remaining solution was loaded in a MICROCON-50<sup>TM</sup> ultrafiltration unit, and spun using program 10 (6 minutes). The filtration unit was inverted over a second tube and spun using program 2 (3 minutes). After the final recovery spin, a total of 100 μl TE was added, then 1 μl of the final product was pipetted on DE81 paper and counted in 6 ml of BIOFLUOR II<sup>TM</sup>.

The probe was run on a TBE/urea gel. A total of 1-3 μl of the probe or 5 μl of RNA Mrk III was added to 3 μl of loading buffer. After heating on a 95°C heat block for three minutes, the gel was immediately placed on ice. The wells of gel were flushed, and the sample was loaded and run at 180-250 volts for 45 minutes. The gel was wrapped in plastic wrap (SARAN<sup>TM</sup> brand) and exposed to XAR film with an intensifying screen in a -70°C freezer one hour to overnight.

### 6.24.2. <sup>33</sup>P-Hybridization

#### 6.24.2.1. *Pretreatment of frozen sections*

The slides were removed from the freezer, placed on aluminum trays, and thawed at room temperature for 5 minutes. The trays were placed in a 55°C incubator for five minutes to reduce condensation. The slides were fixed for 10 minutes in 4% paraformaldehyde on ice in the fume hood, and washed in 0.5 x SSC for 5 minutes, at room temperature (25 ml 20 x SSC + 975 ml SQ H<sub>2</sub>O). After deproteinization in 0.5 µg/ml proteinase K for 10 minutes at 37°C (12.5 µl of 10 mg/ml stock in 250 ml prewarmed RNase-free RNase buffer), the sections were washed in 0.5 x SSC for 10 minutes at room temperature. The sections were dehydrated in 70%, 95%, and 100% ethanol, 2 minutes each.

#### 6.24.2.2. *Pretreatment of paraffin-embedded sections*

The slides were deparaffinized, placed in SQ H<sub>2</sub>O, and rinsed twice in 2 x SSC at room temperature, for 5 minutes each time. The sections were deproteinized in 20 µg/ml proteinase K (500 µl of 10 mg/ml in 250 ml RNase-free RNase buffer; 37°C, 15 minutes) for human embryo tissue, or 8 x proteinase K (100 µl in 250 ml RNase buffer, 37°C, 30 minutes) for formalin tissues. Subsequent rinsing in 0.5 x SSC and dehydration were performed as described above.

#### 6.24.2.3. *Prehybridization*

The slides were laid out in a plastic box lined with Box buffer (4 x SSC, 50% formamide) - saturated filter paper. The tissue was covered with 50 µl of hybridization buffer (3.75 g dextran sulfate + 6 ml SQ H<sub>2</sub>O), vortexed, and heated in the microwave for 2 minutes with the cap loosened. After cooling on ice, 18.75 ml formamide, 3.75 ml 20 x SSC, and 9 ml SQ H<sub>2</sub>O were added, and the tissue was vortexed well and incubated at 42°C for 1-4 hours.

#### 6.24.2.4. *Hybridization*

1.0 x 10<sup>6</sup> cpm probe and 1.0 µl tRNA (50 mg/ml stock) per slide were heated at 95°C for 3 minutes. The slides were cooled on ice, and 48 µl hybridization buffer was added per slide. After vortexing, 50 µl <sup>33</sup>P mix was added to 50 µl prehybridization on the slide. The slides were incubated overnight at 55°C.

#### 6.24.2.5. *Washes*

Washing was done for 2x10 minutes with 2xSSC, EDTA at room temperature (400 ml 20 x SSC + 16 ml 0.25 M EDTA, V<sub>f</sub>=4L), followed by RNaseA treatment at 37°C for 30 minutes (500 µl of 10 mg/ml in 250 ml RNase buffer = 20 µg/ml). The slides were washed 2 x10 minutes with 2 x SSC, EDTA at room temperature. The stringency wash conditions were as follows: 2 hours at 55°C, 0.1 x SSC, EDTA (20 ml 20 x SSC + 16 ml EDTA, V<sub>f</sub>=4L).

6.24.2.6. *Oligonucleotides*

*In situ* analysis was performed on three of the DNA sequences disclosed herein. The primers used to generate the probes and/or the probes employed for these analyses are as follows:

5 DNA33100-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CGG GTG GAG GTG GAA CAG AAA  
3' (SEQ ID NO:375)

DNA33100-p2: 5' CTA TGA AAT TAA CCC TCA CTA AAG GGA CAC AGA CAG AGC CCC ATA CGC  
3' (SEQ ID NO:376)

DNA34431-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CAG GGA AAT CCG GAT GTC TC  
3' (SEQ ID NO:377)

10 DNA34431-p2: 5' CTA TGA AAT TAA CCC TCA CTA AAG GGA GTA AGG GGA TGC CAC CGA GTA  
3' (SEQ ID NO:378)

DNA38268-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CAG CTA CCC GCA GGA GGA GG  
3' (SEQ ID NO:379)

15 DNA38268-p2: 5'CTA TGA AAT TAA CCC TCA CTA AAG GGA TCC CAG GTG ATG AGG TCC AGA  
3' (SEQ ID NO:380)

DNA64908 probe: 5'CCATCTCGGAGACCTTTGTGCAGCGTGTATACCAGCCTTACCTCACCA  
CTTGCGACGGACACAGAGCCTGCAGCACCTACCGAACCATCTACCGGAC  
TGCCTATCGCCGTAGCCCTGGGGTGACTCCCGCAAGCCTCGCTATGCTTG  
CTGCCCTGGTTGGAAGAGGACCAGTGGGCTCCCTGGGGCTTGTGGAGCA  
20 GCAATATGCCAGCCTCCATGTGGAATGGAGGGAGTTGCATCCGCCCAG  
GACACTGCCGCTGCCCTGTGGGATGGCAGGGAGATACTTGCCAGACAGA  
TGTTGATGAATGCAGTACAGGAGAGGCCAGTTGTCCCCAGCGCTGTGTC  
AATACTGTGGGAAGTTACTGGTGCCAGGGATGGGAGGGACAAAGCCCAT  
CTGCAGATGGGACGCGCTGCCTGTCTAAGGAGGGGCCCTCCCGGTGGCC  
25 CCAACCCACAGCAGGAGTGGACAGCA3' (SEQ ID NO:381)

6.24.2.7. *Results*

*In situ* analysis was performed and the results from these analyses are as follows:

6.24.2.7.1. DNA33100-1159 (PRO229) (Scavenger-R/CD6  
homologTNF motif)

A specific positive signal was observed in mononuclear phagocytes (macrophages) of fetal and adult spleen, liver, lymph node and thymus. All other tissues were negative.

5 6.24.2.7.2. DNA34431-1177 (PRO263) (CD44)

A specific positive signal was observed in human fetal tissues and placenta over mononuclear cells, with strong expression in epithelial cells of the adrenal cortex. All adult tissues were negative.

6.24.2.7.3. DNA38268-1188 (PRO295) (Integrin)

10 A specific positive signal was observed in human fetal ganglion cells, fetal neurons, adult adrenal medulla and adult neurons. All other tissues were negative.

6.24.2.7.4. DNA64908-1163-1 (PRO1449)

15 A specific positive signal was observed in the developing vasculature (from E7-E11), in endothelial cells and in progenitors of endothelial cells in wholemount in situ hybridizations of mouse embryos (Figure 375). Specific expression was also observed in a subset of blood vessels and epidermis from E12 onward. A mouse orthologue of PRO1449 which has about 78% amino acid identity with PRO1449 was used as the probe.

In normal adult tissues, expression was low to absent. When present, expression was confined to the vasculature (Figure 376). Figure 376 further shows that highest expression in adult tissues was observed regionally in vessels running within the white matter of the brain. Elevated expression was also observed in vasculature of many inflamed and diseased tissues, including, but not limited to, tumor vasculature.

20 Following electroporation of the mouse orthologue of PRO1449 into the choroid layer in the eyes of chicken embryos, new vessel formation was observed in the electroporated eye (top right), but not in the control side from the same embryo (top left), or an embryo that was electroporated with a control cDNA (bottom right) (Figure 377).

25 The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct(s) deposited, since the deposited embodiment(s) is/are intended as single illustration(s) of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material(s) herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific  
30 illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure

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2. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ

5 ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165), Figure 167 (SEQ ID NO:167), Figure 169 (SEQ ID NO:169), Figure 171 (SEQ ID NO:171), Figure 173 (SEQ ID NO:173), Figure 175 (SEQ ID NO:175), Figure 177 (SEQ ID NO:177), Figure 10 179 (SEQ ID NO:179), Figure 181 (SEQ ID NO:181), Figure 183 (SEQ ID NO:183), Figure 185 (SEQ ID NO:185), Figure 187 (SEQ ID NO:187), Figure 189 (SEQ ID NO:189), Figure 191 (SEQ ID NO:191), Figure 193 (SEQ ID NO:193), Figure 195 (SEQ ID NO:195), Figure 197 (SEQ ID NO:197), Figure 199 (SEQ ID NO:199), Figure 201 (SEQ ID NO:201), Figure 203 (SEQ ID NO:203), Figure 205 (SEQ ID NO:205), Figure 207 (SEQ ID NO:207), Figure 209 (SEQ ID NO:209), Figure 211 (SEQ ID NO:211), Figure 213 (SEQ ID NO:213), Figure 215 (SEQ ID NO:215), Figure 217 (SEQ ID NO:217), Figure 219 (SEQ ID NO:219), Figure 15 221 (SEQ ID NO:221), Figure 223 (SEQ ID NO:223), Figure 225 (SEQ ID NO:225), Figure 227 (SEQ ID NO:227), Figure 229 (SEQ ID NO:229), Figure 231 (SEQ ID NO:231), Figure 233 (SEQ ID NO:233), Figure 235 (SEQ ID NO:235), Figure 237 (SEQ ID NO:237), Figure 239 (SEQ ID NO:239), Figure 241 (SEQ ID NO:241), Figure 243 (SEQ ID NO:243), Figure 245 (SEQ ID NO:245), Figure 247 (SEQ ID NO:247), Figure 20 249 (SEQ ID NO:249), Figure 251 (SEQ ID NO:251), Figure 253 (SEQ ID NO:253), Figure 255 (SEQ ID NO:255), Figure 257 (SEQ ID NO:257), Figure 259 (SEQ ID NO:259), Figure 261 (SEQ ID NO:261), Figure 263 (SEQ ID NO:263), Figure 265 (SEQ ID NO:265), Figure 267 (SEQ ID NO:267), Figure 269 (SEQ ID NO:269), Figure 271 (SEQ ID NO:271), Figure 273 (SEQ ID NO:273), Figure 275 (SEQ ID NO:275), Figure 277 (SEQ ID NO:277), Figure 279 (SEQ ID NO:279), Figure 281 (SEQ ID NO:281), Figure 283 (SEQ ID NO:283), Figure 285 (SEQ ID NO:285), Figure 287 (SEQ ID NO:287), Figures 289A-289B (SEQ ID NO:289), 25 Figure 291 (SEQ ID NO:291), Figure 293 (SEQ ID NO:293), Figure 295 (SEQ ID NO:295), Figure 297 (SEQ ID NO:297), Figure 299 (SEQ ID NO:299), Figure 301 (SEQ ID NO:301), Figure 303 (SEQ ID NO:303), Figure 305 (SEQ ID NO:305), Figure 307 (SEQ ID NO:307), Figure 309 (SEQ ID NO:309), Figures 311A-311B (SEQ ID NO:311), Figure 313 (SEQ ID NO:313), Figure 315 (SEQ ID NO:315), Figure 317 (SEQ ID NO:317), Figure 30 319 (SEQ ID NO:319), Figure 321 (SEQ ID NO:321), Figure 323 (SEQ ID NO:323), Figure 325 (SEQ ID NO:325), Figure 327 (SEQ ID NO:327), Figure 329 (SEQ ID NO:329), Figure 331 (SEQ ID NO:331), Figure 333 (SEQ ID NO:333), Figure 335 (SEQ ID NO:335), Figure 337 (SEQ ID NO:337), Figure 339 (SEQ ID NO:339), Figure 341 (SEQ ID NO:341), Figure 343 (SEQ ID NO:343), Figure 345 (SEQ ID NO:345), Figure 347 (SEQ ID NO:347), Figure 349 (SEQ ID NO:349), Figures 351A-351B (SEQ ID NO:351), Figure 353 (SEQ ID NO:353), Figure 355 (SEQ ID NO:355), Figure 357 (SEQ ID NO:357), Figure 359 (SEQ ID NO:359), Figure 35 361 (SEQ ID NO:361), Figure 363 (SEQ ID NO:363), Figure 365 (SEQ ID NO:365), Figure 367 (SEQ ID NO:367), Figure 369 (SEQ ID NO:369), Figure 371 (SEQ ID NO:371) and Figure 373 (SEQ ID NO:373).

3. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165), Figure 167 (SEQ ID NO:167), Figure 169 (SEQ ID NO:169), Figure 171 (SEQ ID NO:171), Figure 173 (SEQ ID NO:173), Figure 175 (SEQ ID NO:175), Figure 177 (SEQ ID NO:177), Figure 179 (SEQ ID NO:179), Figure 181 (SEQ ID NO:181), Figure 183 (SEQ ID NO:183), Figure 185 (SEQ ID NO:185), Figure 187 (SEQ ID NO:187), Figure 189 (SEQ ID NO:189), Figure 191 (SEQ ID NO:191), Figure 193 (SEQ ID NO:193), Figure 195 (SEQ ID NO:195), Figure 197 (SEQ ID NO:197), Figure 199 (SEQ ID NO:199), Figure 201 (SEQ ID NO:201), Figure 203 (SEQ ID NO:203), Figure 205 (SEQ ID NO:205), Figure 207 (SEQ ID NO:207), Figure 209 (SEQ ID NO:209), Figure 211 (SEQ ID NO:211), Figure 213 (SEQ ID NO:213), Figure 215 (SEQ ID NO:215), Figure 217 (SEQ ID NO:217), Figure 219 (SEQ ID NO:219), Figure 221 (SEQ ID NO:221), Figure 223 (SEQ ID NO:223), Figure 225 (SEQ ID NO:225), Figure 227 (SEQ ID NO:227), Figure 229 (SEQ ID NO:229), Figure 231 (SEQ ID NO:231), Figure 233 (SEQ ID NO:233), Figure 235 (SEQ ID NO:235), Figure 237 (SEQ ID NO:237), Figure 239 (SEQ ID NO:239), Figure 241 (SEQ ID NO:241), Figure 243 (SEQ ID NO:243), Figure 245 (SEQ ID NO:245), Figure 247 (SEQ ID NO:247), Figure 249 (SEQ ID NO:249), Figure 251 (SEQ ID NO:251), Figure



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4. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

5. A vector comprising the nucleic acid of Claim 1.

6. A host cell comprising the vector of Claim 5.

7. The host cell of Claim 6, wherein said cell is a CHO cell.

8. The host cell of Claim 6, wherein said cell is an *E. coli*.

9. The host cell of Claim 6, wherein said cell is a yeast cell.

10. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 6 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID

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12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

13. A chimeric molecule comprising a polypeptide according to Claim 11 fused to a heterologous amino acid sequence.

14. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is an epitope tag sequence.

15. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

16. An antibody which specifically binds to a polypeptide according to Claim 11.

17. The antibody of Claim 16, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

18. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to:

(a) a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26),  
5 Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64),  
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NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure

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(c) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18

(SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure

284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide.

19. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) an amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152),



NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide;

(b) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26

(SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure

292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), with its associated signal peptide; or

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID

NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide.

20. A method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal a therapeutically effective amount of a polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32),

Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure

298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), or agonist or antagonist thereof.

21. The method according to Claim 20, wherein the mammal is human.

22. The method of Claim 21, wherein the human has suffered myocardial infarction.

23. The method of Claim 21, wherein the human has cardiac hypertrophy, trauma, a cancer, or age-related macular degeneration.

24. The method of Claim 23, wherein the cardiac hypertrophy is characterized by the presence of an elevated level of  $\text{PGF}_{2\alpha}$ .

25. The method of Claim 20, wherein the polypeptide is administered together with a cardiovascular, endothelial or angiogenic agent.

26. The method of Claim 23, wherein the polypeptide is administered following primary angioplasty.

27. The method of Claim 20, wherein the cardiovascular, endothelial or angiogenic disorder is cancer.

28. The method of Claim 27, wherein the polypeptide is administered in combination with a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent.

29. The method of Claim 20, wherein said agonist is an antibody to said polypeptide.

30. The method of Claim 20, wherein said antagonist is an antibody to said polypeptide.

31. A method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal a nucleic acid molecule that encodes a polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure

256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), or agonist or antagonist thereof.

32. The method of Claim 31, wherein said agonist is an antibody to said polypeptide.

33. The method of Claim 31, wherein said antagonist is an antibody to said polypeptide.

34. The method of Claim 31, wherein the mammal is human.

35. The method of Claim 31, wherein the nucleic acid molecule is administered via *ex vivo* gene therapy.

36. A method for inhibiting endothelial cell growth in a mammal comprising administering to the mammal a PRO247, PRO720 or PRO4302 polypeptide or agonist thereof, wherein endothelial cell growth in said mammal is inhibited.

37. A method for stimulating endothelial cell growth in a mammal comprising administering to the mammal a PRO21, PRO181, PRO205, PRO214, PRO221, PRO229, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO365, PRO444, PRO533, PRO697, PRO725, PRO771, PRO788, PRO791, PRO819, PRO827, PRO828, PRO836, PRO846, PRO865, PRO1005, PRO1006, PRO1007, PRO1025, PRO1029, PRO1054, PRO1071, PRO1075, PRO1079,



PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1184, PRO1186, PRO1190, PRO1192, PRO1195, PRO1244, PRO1272, PRO1273, PRO1274, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1411, PRO1412, PRO1419, PRO1474, PRO1477, PRO1488, PRO1508, PRO1550, PRO1556, PRO1760, PRO1782, PRO1787, PRO1801, PRO1868, PRO1887, PRO1890, PRO3438, PRO3444, PRO4302, PRO4324, PRO4333, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4405, PRO4408, PRO4422, PRO4425, PRO4499, PRO5723, PRO5725, PRO5737, PRO5776, PRO6006, PRO6029, PRO6071, PRO7436, PRO9771, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21055, PRO21384 or PRO28631 polypeptide, or agonist thereof, wherein endothelial cell growth in said mammal is stimulated.

38. A method for inducing cardiac hypertrophy in a mammal comprising administering to the mammal a PRO21 polypeptide or agonist thereof, wherein cardiac hypertrophy in said mammal is induced.

39. A method for stimulating angiogenesis induced by a PRO1376 or PRO1449 polypeptide in a mammal comprising administering a therapeutically effective amount of said polypeptide to the mammal, wherein said angiogenesis is stimulated.

40. A method for inducing endothelial cell apoptosis comprising administering to the endothelial cell a PRO4302 polypeptide or agonist thereof, wherein apoptosis in said endothelial cell is induced.

41. A method for stimulating smooth muscle cell growth comprising administering to the smooth muscle cell a PRO162, PRO181, PRO182, PRO195, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1080, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1265, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1309, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1488, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4302, PRO4333, PRO4345, PRO4353, PRO4354, PRO4405, PRO4408, PRO4430, PRO4503, PRO5725, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 or PRO21366 polypeptide, or agonist thereof, wherein smooth muscle cell growth in said smooth muscle cell is stimulated.

42. A method for inducing endothelial cell tube formation comprising administering to the endothelial cell a PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873, PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 or PRO7261 polypeptide, or agonist thereof, wherein tube formation in said endothelial cell is induced.

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**FIGURE 1**

CCCCACGCGTCCGATGGCGTTACGTTTCGCGGCCTTCTGCTACATGCTGGCGCTGCTGCT  
CACTGCCGCGCTCATCTTCTTCGCCATTTGGCACATTATAGCATTTGATGAGCTGAAGAC  
TGATTACAAGAATCCTATAGACCAGTGTAATACCCTGAATCCCCTTGTAAGTCCCAGAGTA  
CCTCATCCACGCTTCTTCTGTGTCATGTTTCTTTGTGCAGCAGAGTGGCTTACACTGGG  
TCTCAATATGCCCCCTTTGGCATATCATATTTGGAGGTATATGAGTAGACCAGTGATGAG  
TGGCCAGGACTCTATGACCCTACAACCATCATGAATGCAGATATTCTAGCATATTGTCA  
GAAGGAAGGATGGTGCAAATTAGCTTTTTTATCTTCTAGCATTTTTTTTACTACCTATATGG  
CATGATCTATGTTTTGGTGAGCTCTTAGAACAACACACAGAAGAATTGGTCCAGTTAAGT  
GCATGCAAAAAGCCACCAAATGAAGGGATTCTATCCAGCAAGATCCTGTCCAAGAGTAGC  
CTGTGGAATCTGATCAGTTACTTTAAAAAATGACTCCTTATTTTTTAAATGTTTCCACAT  
TTTTGCTTGTGGAAAGACTGTTTTCATATGTTATACTCAGATAAAGATTTTTAAATGGTAT  
TACGTATAAATTAATATAAAATGATTACCTCTGGTGTGACAGGTTTGAAGTTGCACTTC  
TTAAGGAACAGCCATAATCCTCTGAATGATGCATTAATTACTGACTGTCCTAGTACATTG  
GAAGCTTTTGTTTATAGGAAGTTGTAGGGCTCATTTTGGTTTCATTGAAACAGTATCTAA  
TTATAAATTAGCTGTAGATATCAGGTGCTTCTGATGAAGTGAAAATGTATATCTGACTAG  
TGGGAAAGTTTATGGGTTTCCTCATCTGTGTCATGTCGATGATTATATATGGATACATTTAC  
AAAAATAAAAAGCGGGAATTTTCCCTTCGCTTGAATATTATCCCTGTATATTGCATGAAT  
GAGAGATTTCCCATATTTCCATCAGAGTAATAAATATACTTGCTTTAATTCTTAAGCATA  
AGTAAACATGATATAAAAAATATATGCTGAATTACTTGTGAAGAATGCATTTAAAGCTATT  
TTAAATGTGTTTTTATTTGTAAGACATTACTTATTAAGAAATTGGTTATTATGCTTACTG  
TTCTAATCTGGTGGTAAAGGTATTCTTAAGAATTTGCAGGTACTACAGATTTTCAAACT  
GAATGAGAGAAAATTGTATAACCATCCTGCTGTTCTTTAGTGCAATACAATAAACTCT  
GAAATTAAGACTC

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**FIGURE 2**

MAFTFAAFCYMLALLLTAAALIFFAIWHIIAFDELKTDYKNPIDQCNTLNPLVLPEYLIHA  
FFCVMFLCAAEWLTGLNMPLLAYHIWRYMSRPVMSGPLYDPTTIMNADILAYCQKEGW  
CKLAFYLLAFFYYLYGMIYVLVSS

**Important features:**

**Signal peptide:**

amino acids 1-20

**Type II transmembrane domain:**

amino acids 11-31

**Other transmembrane domain:**

amino acids 57-77 and 123-143

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**FIGURE 3**

GGCTCAGAGGCCCCACTGGACCCTCGGCTCTTCCTTGGACTTCTTGTGTGTTCTGTGAGC  
TTCGCTGGATT CAGGGTCTTGGGCATCAGAGGTGAGAGGGTGGGAAGGTCCGCCGCGATG  
GGGAAGCCCTGGCTGCGTGCGCTACAGCTGCTGCTCCTGCTGGGCGCGTCGTGGGCGCGG  
GCGGGCGCCCCGCGCTGCACCTACACCTTCGTGCTGCCCCCGCAGAAGTTCACGGGCGCT  
GTGTGCTGGAGCGGCCCCGCATCCACGCGGGCGACGCCCGAGGCCGCCAACGCCAGCGAG  
CTGGCGGCGCTGCGCATGCGCGTCGGCCGCCACGAGGAGCTGTTACGCGAGCTGCAGAGG  
CTGGCGGCGGGCCGACGGCGCCGTGGCCGGCGAGGTGCGCGCGCTGCGCAAGGAGAGCCGC  
GGCCTGAGCGCGCGCCTGGGCCAGTTGCGCGCGCAGCTGCAGCACGAGGCGGGGCCCGGG  
GCGGGCCCGGGGGCGGATCTGGGGGCGGAGCCTGCCGCGGCGCTGGCGCTGCTCGGGGAG  
CGCGTGCTCAACGCGTCCGCCGAGGCTCAGCGCGCAGCCGCCCGGTTCCACCAGCTGGAC  
GTCAAGTTCGCGAGCTGGCGCAGCTCGTCACCCAGCAGAGCAGTCTCATCGCCCGCCTG  
GAGCGCCTGTGCCCCGGGAGGCGCGGGCGGGCAGCAGCAGGTCTGCCGCCACCCCCACTG  
GTGCCTGTGGTTCCGGTCCGTCTTGTGGGTAGCACCAAGTACACCAAGTACAGTGGAC  
CCAGCCCCAGAGCCCCAGAGAGACCAGACCCAGAGACAGCAGGAGCCCATGGCTTCTCCC  
ATGCCTGCAGGTACCCCTGCGGTCCCCACCAAGCCTGTGGGCCCGTGGCAGGATTGTGCA  
GAGGCCCGCCAGGCAGGCCATGAACAGAGTGGAGTGTATGAACTGCGAGTGGGCCGTAC  
GTAGTGT CAGTATGGTGTGAGCAGCAACTGGAGGGTGGAGGCTGGACTGTGATCCAGCGG  
AGGCAAGATGGTT CAGTCAACTTCTTCACTACCTGGCAGCACTATAAGGCGGGCTTTGGG  
CGGCCAGACGGAGAATACTGGCTGGGCCTTGAACCCGTGTATCAGCTGACCAGCCGTGGG  
GACCATGAGCTGCTGGTTCTCCTGGAGGACTGGGGGGGCGGTGGAGCACGTGCCCACTAT  
GATGGCTTCTCCCTGGAACCCGAGAGCGACCACTACCGCCTGCGGCTTGGCCAGTACCAT  
GGTGTATGCTGGAGACTCTCTTTCTGGCACAATGACAAGCCCTTCAGCACCGTGGATAGG  
GACCGAGACTCCTATTCTGGTAACTGTGCCCTGTACCAGCGGGGAGGCTGGTGGTACCAT  
GCCTGTGCCCACTCCAACCTCAACGGTGTGTGGCACCACGGCGGCCACTACCGAAGCCGC  
TACCAGGATGGTGTCTACTGGGCTGAGTTTCGTGGTGGGGCATATTCTCTCAGGAAGGCC  
GCCATGCTCATTCGGCCCCCTGAAGCTGTGACTCTGTGTTCTCTGTCCCCTAGGCCCTAG  
AGGACATTGGTCAGCAGGAGCCCAAGTTGTTCTGGCCACACCTTCTTTGTGGCTCAGTGC  
CAATGTGTCCACAGAACTTCCCACTGTGGATCTGTGACCCTGGGCGCTGAAAATGGGAC  
CCAGGAATCCCCCGCTCAATATCTTGGCCTCAGATGGCTCCCCAAGGTCATTCATATCT  
CGGTTTGAGCTCATATCTTATAATAACACAAAGTAGCCAC

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**FIGURE 4**

MGKPWLRLAQLLLLLGASWARAGAPRCTYTFVLPPQKFTGAVCWSGPASTRATPEAANAS  
ELAALRMVRGRHEELLELRELQRLAAADGAVAGEVRALRKESRGLSARLGQLRAQLQHEAGP  
GAGPGADLGAEPAAALALLGERVLNASAEQAQAAARFHQLDVKFRELAQLVTOQSSLIAR  
LERLCPPGGAGGQQQVLPPPPLVPVVPVRLVGSTSDTSRMLDPAPEPQRDQTORQQEPMAS  
PMPAGHPAVPTKPVGPWQDCAEARQAGHEQSGVYELRVGRHVSVWCEQQLEGGGWTVIQ  
RRQDGSVNFFTTWQHYKAGFGRPDGEYWLGLEPVYQLTSRGDHELLVLLEDWGGRGARAH  
YDGFSLEPESDHYRLRLGQYHGDAGDSLWHNDKPFSTVDRDRDSYSGNCALYQRGGWWY  
HACAHSNLNGVWHHGGHYRSRYQDGVYWAEFRGGAYSLRKAAMLIRPLKL

**Signal peptide:**

Amino acids 1-20

**N-glycosylation sites:**

Amino acids 58-62;145-149

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

Amino acids 97-101

**Tyrosine kinase phosphorylation site:**

Amino acids 441-448

**N-myristoylation sites:**

Amino acids

16-22;23-29;87-93;108-114;121-127;125-131;129-135;187-193;29  
3-299;353-359;378-384;445-451;453-459**Cell attachment sequence:**

Amino acids 340-343

**Fibrinogen beta and gamma chains C-terminal domain signature:**

Amino acids 418-431

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**FIGURE 5**

CCCACGCGTCCGGCGCCGTGGCCTCGCGTCCATCTTTGCCGTTCTCTCGGACCTGTCACA  
AAGGAGTCGCGCCGCCGCCGCCGCCCTCCCTCCGGTGGGCCCCGGGAGGTAGAGAAAGT  
CAGTGCCACAGCCCGACCGCGCTGCTCTGAGCCCTGGGCACGCGGAACGGGAGGGAGTCT  
GAGGGTTGGGGACGTCTGTGAGGGAGGGGAACAGCCGCTCGAGCCTGGGGCGGGCGGACC  
GGACTGGGGCCGGGGTAGGCTCTGGAAGGGCCCGGGAGAGAGGTGGCGTTGGTCAGAAC  
CTGAGAAACAGCCGAGAGGTTTTCCACCGAGGCCCGCGCTTGAGGGATCTGAAGAGGTTT  
CTAGAAGAGGGTGTTCCCTCTTTCCGGGGGTCCTCACCAGAAGAGGTTCTTGGGGGTCGCC  
CTTCTGAGGAGGCTGCGGCTAACAGGGCCAGAACTGCCATTGGATGTCCAGAATCCCCT  
GTAGTTGATAATGTTGGGAATAAGCTCTGCAACTTTCTTTGGCATTTCAGTTGTTAAAAAC  
AAATAGGATGCAAATTCCTCAACTCCAGGTTATGAAAACAGTACTTGGAAGAACTGAAAAC  
TACCTAAATGATCGTCTTTGGTTGGGCCGTGTTCTTAGCGAGCAGAAGCCTTGGCCAGGG  
TCTGTTGTTGACTCTCGAAGAGCACATAGCCCACTTCCTAGGGACTGGAGGTGCCGCTAC  
TACCATGGGTAATTCCTGTATCTGCCGAGATGACAGTGGAACAGATGACAGTGTTGACAC  
CCAACAGCAACAGGCCGAGAACAGTGACAGTACCCACTGCTGACACAAGGAGCCAACCACG  
GGACCCTGTTCCGCCACCAAGGAGGGGCCGAGGACCTCATGAGCCAAGGAGAAAGAAACA  
AAATGTGGATGGGCTAGTGTTGGACACACTGGCAGTAATACGGA CTCTTGTAGATAAGTA  
AGTATCTGACTCACGGTCACCTCCAGTGGAATGAAAAGTGTTCTGCCCCGGAACCATGACT  
TTAGGACTCCTTCAGTTCCTTTAGGACATACTCGCCAAGCCTTGCTGCTCACAGGGCAAAG  
GAGAATATTTTAATGCTCCGCTGATGGCAGAGTAAATGATAAGATTTGATGTTTTTGCTT  
GCTGTCATCTACTTTGTCTGGAATGTCTAAATGTTTCTGTAGCAGAAAACACGATAAAG  
CTATGATCTTTATTAGAG

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**FIGURE 6**

MIVFGWAVFLASRSLGQGLLLTLEEHIAHFLGTGGAATTMGNSCICRDDSGTDDSVDTQQ  
QQAENSAVPTADTRSQPRDPVRPPRRGRGPHEPRRKKQNV DGLVLDTLAVIRTLVDKO

**Signal peptide:**  
amino acids 1-16

**Casein kinase II phosphorylation site:**  
amino acids 22-26, 50-54, 113-117

**N-myristoylation site:**  
amino acids 18-24, 32-38, 34-40, 35-41, 51-57

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**FIGURE 7**

CGGACGCGTGGGGGAAACCCCTTCCGAGAAAACAGCAACAAGCTGAGCTGCTGTGACAGAG  
GGGAACAAGATGGCGGCGCCGAAGGGGAGCCTCTGGGTGAGGACCCAACTGGGGCTCCCG  
CCGCTGCTGCTGCTGACCATGGCCTTGGCCGGAGGTTTCGGGGACCGCTTCGGCTGAAGCA  
TTTGACTCGGTCTTGGGTGATACGGCGTCTTGCCACCGGGCCTGTCAGTTGACCTACCCC  
TTGCACACCTACCCTAAGGAAGAGGAGTTGTACGCATGTCAGAGAGGTTGCAGGCTGTTT  
TCAATTTGTCAGTTTGTGGATGATGGAATTGACTTAAATCGAACTAAATTGGAATGTGAA  
TCTGCATGTACAGAAGCATATTCCTCAATCTGATGAGCAATATGCTTGCCATCTTGTTGC  
CAGAATCAGCTGCCATTCGCTGAACTGAGACAAGAACAACCTTATGTCCCTGATGCCAAA  
ATGCACCTACTCTTTCCTCTAACTCTGGTGAGGTCATTCTGGAGTGACATGATGGACTCC  
GCACAGAGCTTCATAACCTCTTCATGGACTTTTTATCTTCAAGCCGATGACGGAAAAATA  
GTTATATTCCAGTCTAAGCCAGAAATCCAGTACGCACCACATTTGGAGCAGGAGCCTACA  
AATTTGAGAGAATCATCTCTAAGCAAAATGTCTTATCTGCAAATGAGAAATTCACAAGCG  
CACAGGAATTTTCTTGAAGATGGAGAAAGTGATGGCTTTTTAAGATGCCTCTCTCTTAAC  
TCTGGGTGGATTTTAACTACAACCTCTTGTCCTCTCGGTGATGGTATTGCTTTGGATTTGT  
TGTGCAACTGTTGCTACAGCTGTGGAGCAGTATGTTCCCTCTGAGAAGCTGAGTATCTAT  
GGTGACTTGGAGTTTATGAATGAACAAAAGCTAAACAGATATCCAGCTTCTTCTCTTG  
GTTGTTAGATCTAAACTGAAGATCATGAAGAAGCAGGGCCTCTACCTACAAAAGTGAAT  
CTTGCTCATTCTGAAATTTAAGCATTTTTCTTTTAAAAGACAAGTGTAATAGACATCTAA  
AATCCACTCCTCATAGAGCTTTTAAAATGGTTTCATTGGATATAGGCCTTAAGAAATCA  
CTATAAAATGCAAATAAAGTTACTCAAATCTGTG



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**FIGURE 8**

MAAPKGS LWVRTQLGLPPLLLLTMALAGGSGTASAEAFDSVLGDTASCHRAQQLTYPLHT  
YPKEEELYACQRCRLFSICQFVDDGIDLNRKLECESACTEAYSQSDEQYACHLGCONQ  
LPFAELRQEQMLSLMPKMHLFPPLTLVRSFWSMMDSAQSFITSSWTFYLQADDGKIVIF  
QSKPEIQYAPHLEQEPTNLRESSLSKMSYLMRNSQAHRNFLEDGESDGFRLCLSLNSGW  
ILTTTLVLSVMVLLWICCATVATAVEQYVPSEKLSIYGDLEFMNEQKLNRYPASSLVVVR  
SKTEDHEEAGPLPTKVNLAHSEI

**Important features:**

**Signal peptide:**

amino acids 1-31

**Transmembrane domain:**

amino acids 241-260

**N-glycosylation site:**

amino acids 90-93

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**FIGURE 9**

TATTTACCATATCAGATTCACATTCAGTCCTCAGCAAAATGAAGGGCTCCATTTTCACTC  
TGTTTTTATTCTCTGTCCTATTTGCCATCTCAGAAGTGCGGAGCAAGGAGTCTGTGAGAC  
TCTGTGGGCTAGAATACATACGGACAGTCATCTATATCTGTGCTAGCTCCAGGTGGAGAA  
GGCATCTGGAGGGGATCCCTCAAGCTCAGCAAGCTGAGACAGGAACTCCTTCCAGCTCC  
CACATAAACGTGAGTTTTCTGAGGAAAATCCAGCGCAAAACCTTCCGAAGGTGGATGCCT  
CAGGGGAAGACCGTCTTTGGGGTGGACAGATGCCCACTGAAGAGCTTTGGAAGTCAAAGA  
AGCATTCAAGTGATGTCAAGACAAGATTTACAACTTTGTGTTGCACTGATGGCTGTTCCA  
TGACTGATTTGAGTGCTCTTTGCTAAGACAAGAGCAAATACCCAATGGGTGGCAGAGCTT  
TATCACATGTTTAATTACAGTGTTTTACTGCCTGGTAGAACACTAATATTGTGTTATTAA  
AATGATGGCTTTTGGGTAGGCAAACTTCTTTTCTAAAAGGTATAGCTGAGCGGTGAAA  
CCACAGTGATCTCTATTTTCTCCCTTTGCCAAGGTTAATGAACTGTTCTTTTCAAATTCT  
ACTAATGCTTTGAAATTTCAAATGCTGCGCAAAATTGCAATAAAAATGCTATAAA

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**FIGURE 10**

MKGSIFTLFLFSVLFAISEVRSKESVRLCGLEYIRTVIYICASSRWRRLHLEGI PQAQQAE  
TGNSFQLPHKREFSEENPAQNLPKVDASGEDRLWGGQMPTEELWKS KKHVMSRQDLQTL  
CCTDGCSMTDLSALC

**Important features:****Signal sequence:**

amino acids 1-18

**cAMP- and cGMP-dependent protein kinase phosphorylation  
site:**

amino acids 107-111

**N-myristoylation sites:**

amino acids 3-9,52-58,96-102,125-131

**Insulin family signature:**

amino acids 121-136

**Insulin family proteins:**

amino acids 28-46

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**FIGURE 11**

CCCACGCGTCCGGACAAACTGGAGGTGAAAGGAGCTGGTACTGTCCACTGTGCTGTCCGGT  
GCTGAACCTGAGACGCGAGCGGACCAAGTTGCTCCAGCACCTGAAGGCAACGCCCTCTTGC  
ACCCTCTGTGCCCTGTGGGACCCGCTTCACCAACAGGACCCATATCAACTTGACAAAGGA  
GTGTGGTATCGGACGTGGGAGAGAGTCTCTGTTTGCCACCTGGGCGCTCATTGAGGCGT  
GACTTTGGAGATTTCTATAGTTTTAGACCAAACCTATTTTTTTTTTCCCCAGCTAAGACGAT  
CTTTTGAGAGTTTTTTTTTTTTTATTGTGATTTATATTTCCACAGCGTTTAGGAATCTTTCT  
GGGGGACTTTTGTGACTGTAAATAAGGTGAAAAGCAATAAGGATGTTTAAGTGCTGGT  
CAGTTGTCTTGGTTCTCGGATTCATTTTTCTGGAGTCGGAAGGAAGGCCAACCAAAGAAG  
GAGGATATGGCCTTAAATCCTATCAGCCTCTAATGAGATTGCGACATAAGCAGGAAAAAA  
ATCAAGAAAGTTCAAGAGTCAAAGGATTTATGATTCAGGATGGCCCTTTTGGATCTTGTG  
AAAATAAGTACTGTGGTTTGGGAAGACACTGTGTTACCAGCAGAGAGACAGGGCAAGCAG  
AATGTGCCTGTATGGACCTTTGCAAACGTCCTACAAACCTGTGTGTGGATCTGACGGAG  
AATTCTATGAAAACCACTGTGAAGTGCACAGAGCTGCTTGCCTGAAAAAACAAAAGATTA  
CCATTGTTACAATGAAGACTGCTTCTTTAAAGGAGATAAGTGCAAGACTACTGAATACA  
GCAAGATGAAAAATATGCTATTAGATTTACAAATCAAAAATATATTATGCAAGAAAATG  
AAAATCCTAATGGCGACGACATATCTCGGAAGAAGCTATTGGTGGATCAAATGTTTAAAT  
ATTTTGATGCAGACAGTAATGGACTTGTAGATATTAATGAACTAACTCAGGTGATAAAAC  
AGGAAGAACTTGGCAAGGATCTCTTTGATTGTACTTTGTATGTTCTATTGAAATATGATG  
ATTTTAATGCTGACAAGCACCTGGCTCTTGAAGAATTTTATAGAGCATTCCAAGTGATCC  
AGTTGAGTCTGCCAGAAGATCAGAACTAAGCATCACTGCAGCAACTGTGGGACAAAGTG  
CTGTTCTGAGCTGTGCCATTCAAGGAACCCTGAGACCTCCCATTATCTGGAAAAGGAACA  
ATATTATTCTAAATAATTTAGATTTGGAAGACATCAATGACTTTGGAGATGATGGGTCCT  
TGTATATTACTAAGGTTACCACAACTCACGTTGGCAATTACACCTGCTATGCAGATGGCT  
ATGAACAAGTCTATCAGACTCACATCTTCCAAGTGAATGTTCTCCTCCAGTCATCC

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**FIGURE 12**

MFKCWSVVLVLGFIFLESEGRPTKEGGYGLKSYQPLMRLRHKQEKQESSRVKGFMIQDG  
PFGSCENKYCGLGRHCVTSRETGQAECACMDLCKRHYKPVCSDGEFYENHCEVHRAACL  
KKQKITIVHNEDCFFKGDCKTTEYSKMKNMLLDLQNQKYIMQENENPNGDDISRKKLLV  
DQMFKYFDADSNGLVDINELTQVIKQEELGKDLFDCTLYVLLKYDDFNADKHLALEEFYR  
AFQVIQLSLPEDQKLSITAATVGQSAVLSCAIQGTLRPPIIWKRNNIILNNLDLEDINDF  
GDDGSLYITKVTTHVGNVTCYADGYEQVYQTHIFQVNVPPVI

**Signal sequence:**

Amino acids 1-20

**N-glycosylation site:**

Amino acids 318-322

**Tyrosine kinase phosphorylation sites:**

Amino acids 21-29;211-220

**N-myristoylation sites:**

Amino acids 63-69;83-89;317-323

**Prokaryotic membrane lipoprotein lipid attachment site:**

Amino acids 260-271

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**FIGURE 13**

TGCCGGGCTGCGGGGCGCCTTGACTCTCCCTCCACCCTGCCTCCTCGGGCTCCACTCGTC  
TGCCCCTGGA CTCCCGTCTCCTCCTGTCTCCGGCTTCCCAGAGCTCCCTCCTTATGGCA  
GCAGCTTCCCGCGTCTCCGGCGCAGCTTCTCAGCGGACGACCCTCTCGCTCCGGGGCTGA  
GCCAGTCCCTGGATGTTGCTGAAACTCTCGAGATCATGCGCGGGTTTGGCTGCTGCTTC  
CCCGCCGGGTGCCACTGCCACCGCCGCCGCTCTGCTGCCGCCGTCCGCGGGATGCTCAG  
TAGCCCGCTGCCCGGCCCCCGCGATCCTGTGTTCTCGGAAGCCGTTTGCTGCTGCAGAG  
TTGCACGAACTAGTCATGGTGTGTGGGAGTCCCCGCGGCAGTGCAGCAGCTGGACACTT  
TGCGAGGGCTTTTGCTGGCTGCTGCTGCTGCCCGTCATGCTACTCATCGTAGCCCGCCCG  
GTGAAGCTCGCTGCTTTCCCTACCTCCTTAAGTGACTGCCAAACGCCCACCGGCTGGAAT  
TGCTCTGTTTATGATGACAGAGAAAATGATCTCTTCCTCTGTGACACCAACACCTGTAAA  
TTTGATGGGGAATGTTTAAGAATTGGAGACACTGTGACTTGCGTCTGTGAGTTCAAGTGC  
AACAATGACTATGTGCCTGTGTGTGGCTCCAATGGGGAGAGCTACCAGAATGAGTGTTAC  
CTGCGACAGGCTGCATGCAAACAGCAGAGTGAGATACTTGTGGTGTGAGAAGGATCATGT  
GCCACAGATGCAGGATCAGGATCTGGAGATGGAGTCCATGAAGGCTCTGGAGAACTAGT  
CAAAGGAGACATCCACCTGTGATATTTGCCAGTTTGGTGCAGAATGTGACGAAGATGCC  
GAGGATGTCTGGTGTGTGTGTAATATTGACTGTTCTCAAACCAACTTCAATCCCCTCTGC  
GCTTCTGATGGGAAATCTTATGATAATGCATGCCAAATCAAAGAAGCATCGTGTCAGAAA  
CAGGAGAAAATTGAAGTCATGTCTTTGGGTCGATGTCAAGATAACACAACACTACAACACT  
AAGTCTGAAGATGGGCATTATGCAAGAACAGATTATGCAGAGAATGCTAACAAATTAGAA  
GAAAGTGCCAGAGAACACCACATACCTTGTCCGGAACATTACAATGGCTTCTGCATGCAT  
GGGAAGTGTGAGCATTCTATCAATATGCAGGAGCCATCTTGCAGGTGTGATGCTGGTTAT  
ACTGGACAACACTGTGAAAAAAGGACTACAGTGTTCTATACGTTGTTCCCGGTCCTGTA  
CGATTTTCAGTATGTCTTAATCGCAGCTGTGATTGGAACAATTCAGATTGCTGTCATCTGT  
GTGGTGGTCCTCTGCATCACAAGGAAATGCCCCAGAAGCAACAGAATTCACAGACAGAAG  
CAAATAACAGGGCACTACAGTTCAGACAATAACAAGAGCGTCCACGAGGTTAATCTAA  
AGGGAGCATGTTTCACAGTGGCTGGACTACCGAGAGCTTGGACTACACAATACAGTATTA  
TAGACAAAAGAATAAGACAAGAGATCTACACATGTTGCCTTGCAATTTGTGGTAATCTACA  
CCAATGAAAACATGTACTACAGCTATATTTGATTATGTATGGATATATTTGAAATAGTAT  
ACATTGTCTTGATGTTTTTTCTGTAATGTAAATAAATACTATTTATATCACACAATATAGTT  
TTTTCTTTCCCATGTATTTGTTATATATAATAAATACTCAGTGATGAG

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**FIGURE 14**

MVLWESPRQCSSWTLCEGFCWLLLLPVMLLIVARPVKLAAFPSTLSDCQTPTGWNC SGY  
DDRENDLFLCDTNTCKFDGECLRIGDTVTCVCQFKCNNDYVPVCGSNGESYQNECYLRQ  
AACKQQSEILVVSEGSCATDAGSGSGDGVHEGSGETSQKETSTCDICQFGAECDEDAED  
VWCVCNIDCSQTNFNPLCASDGKSYDNACQIKEASCQKQEKIEVMSLGRCQDNTTTT TK  
SEDGHYARTDYAENANKLEESAREHHIPCPEHYNGFCMHGKCEHSINMQEPSCRC DAGY  
TGQHCEKKDYSVLYVVPGPVRFQYVLIAAVIGTIQIAVICVVVLCITRK CPRSNRIHRQ  
KQNTGHYSSDNTTRASTRLI

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**FIGURE 15**

GGAGCTCAGCCCAGTGGGCAGTCTGAAGATGGCCAATTACACGCTGGCACCAGAGGATGA  
ATATGATGTCCTCATAGAAGGTGAACTGGAGAGCGATGAGGCAGAGCAATGTGACAAGTA  
TGACGCCCAGGCACCTCTCAGCCCAGCTGGTGCCATCACTCTGCTCTGCTGTGTTTGTGAT  
CGGTGTCCTGGACAATCTCCTGGTTGTGCTTATCCTGGTAAATATAAAGGACTCAAACG  
CGTGGAAAATATCTATCTTCTAAACTTTGGCAGTTTCTAACTTGTGTTTCTTGCTTACCCT  
GCCCTTCTGGGCTCATGCTGGGGGCGATCCCATGTGTAAATTTCTCATTGGACTGTACTT  
CGTGGGCCTGTACAGTGAGACATTTTTCAATTGCCTTCTGACTGTGCAAAGGTACCTAGT  
GTTTTTGCACAAGGGCAACTTTTTCTCAGCCAGGAGGAGGGTGCCCTGTGGCATCATTAC  
AAGTGTCTTGGCATGGGTAAACAGCCATTCTGGCCACTTTGCCTGAATACGTGGTTTATAA  
ACCTCAGATGGAAGACCAGAAATACAAGTGTGCATTTAGCAGAACTCCCTTCTGCCAGC  
TGATGAGACATTCTGGAAGCATTTTCTGACTTTAAAAATGAACATTTTCGGTTCTTGTCTT  
CCCCCTATTTATTTTTACATTTCTCTATGTGCAAATGAGAAAAACACTAAGGTTTCAGGGA  
GCAGAGGTATAGCCTTTTCAAGCTTGTTTTTGCCATAATGGTAGTCTTCCTTCTGATGTG  
GGCGCCCTACAATATTGCATTTTTCTGTCCACTTTCAAAGAACACTTCTCCCTGAGTGA  
CTGCAAGAGCAGCTACAATCTGGACAAAAGTGTTACATCACTAACTCATCGCCACCAC  
CCTGCTGCATCAACCCTCTCCTGTATGCGTTTCTTGATGGGACATTTAGCAAATACCT  
CTGCCGCTGTTTCCATCTGCGTAGTAACACCCCACTTCAACCCAGGGGGCAGTCTGCACA  
AGGCACATCGAGGGAAGAACCTGACCATTCCACCGAAGTGTA~~AA~~ACTAGCATCCACCAAAT  
GCAAGAAGAATAAACATGGATTTTCATCTTTCTGCATTATTTTCATGTAAATTTTCTACAC  
ATTTGTATACAAAATCGGATACAGGAAGAAAAGGGAGAGGTGAGCTAACATTTGCTAAGC  
ACTGAATTTGTCTCAGGCACCGTGCAAGGCTCTTTACAAACGTGAGCTCCTTCGCCTCCT  
ACCACTTGTCCATAGTGTGGATAGGACTAGTCTCATTTCTCTGAGAAGAAAATAAGGCG  
CGGAAATTTGTCTAAGATCACATAACTAGGAAGTGGCAGAACTGATTCTCCAGCCCTGGT  
AGCATTTGCTCAGAGCCTACGCTTGGTCCAGAACATCAAACCTCAAACCCTGGGGACAAA  
CGACATGAAATAAATGTATTTTAAACATCTAAAA



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**FIGURE 16**

MANYTLAPEDEYDVLIEGELESDEAEQCDKYDAQALSAQLVPSLCSAVFVIGVLDNLLVV  
LILVKYKGLKRVENIYLLNLAVSNLCFLLTLPFWAHAGGDPCKILIGLYFVGLYSETFF  
NCLLTVQRYLVFLHKGNNFSARRRVPCGIITSVLAWVTAILATLPEYVVYKPMEDQKYK  
CAFSRTPFLPADETFWKHFLTLKMNISVLVLPLFI FTFLYVQMRKTLRFREQRYSLFKLV  
FAIMVVFLLMWAPYNIAFFLSTFKEHFSLSDCSSYNLDKSVHITKLIATTHCCINPLLY  
AFLDGTFSKYLRCRCFHLRSNTPLQPRGQSAQGTSSREEPDHSTEV

**Signal sequence:**

None

**Transmembrane domain:**

41-61, 76-96, 109-129, 147-167, 199-219, 237-257, 285-305

**7 transmembrane receptor (rhodopsin family):**

55-300

**N-glycosylation site:**

3-6, 205-208

**Tyrosine kinase phosphorylation site:**

70-76, 171-179, 228-234

**N-myristoylation site:**

52-57, 136-141, 148-153

**G-protein coupled receptors:**

55-85, 96-136, 209-220, 235-254, 292-308

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**FIGURE 17**

CGGACGCGTG GGGCGGACGCGTG GGGCGGCCACGGCGCCCGCGGGCTGGGGCGGTGCTTC  
TTCCTTCTCCGTGGCCTACGAGGGTCCCCAGCCTGGGTAAAGATGGCCCCATGGCCCCCG  
AAGGGCCTAGTCCCAGCTGTGCTCTGGGGCCTCAGCCTCTTCCTCAACCTCCCAGGACCT  
ATCTGGCTCCAGCCCTCTCCACCTCCCAGTCTTCTCCCCCGCCTCAGCCCCATCCGTGT  
CATACCTGCCGGGGACTGGTTGACAGCTTTAACAAGGGCCTGGAGAGAACCATCCGGGAC  
AACTTTGGAGGTGGAAACACTGCCTGGGAGGAAGAGAATTTGTCCAAATACAAAGACAGT  
GAGACCCGCCTGGTAGAGGTGCTGGAGGGTGTGTGCAGCAAGTCAGACTTCGAGTGCCAC  
CGCCTGCTGGAGCTGAGTGAGGAGCTGGTGGAGAGCTGGTGGTTTCACAAGCAGCAGGAG  
GCCCCGGACCTCTTCCAGTGGCTGTGCTCAGATTCCCTGAAGCTCTGCTGCCCCGCAGGC  
ACCTTCGGGGCCCTCCTGCCTTCCCTGTCTGGGGGAACAGAGAGGCCCTGCGGTGGCTAC  
GGGCAGTGTGAAGGAGAAGGGACACGAGGGGGCAGCGGGCACTGTGACTGCCAAGCCGGC  
TACGGGGGTGAGGCCTGTGGCCAGTGTGGCCTTGGCTACTTTGAGGCAGAACGCAACGCC  
AGCCATCTGGTATGTTCCGCTTGTTTTGGCCCCCTGTGCCCCGATGCTCAGGACCTGAGGAA  
TCAAACCTGTTTGCAATGCAAGAAGGGCTGGGCCCTGCATCACCTCAAGTGTGTAGACATT  
GATGAGTGTGGCACAGAGGGAGCCAACTGTGGAGCTGACCAATTCTGCGTGAACACTGAG  
GGCTCCTATGAGTGCCGAGACTGTGCCAAGGCCTGCCTAGGCTGCATGGGGGCAGGGCCA  
GGTCGCTGTAAGAAGTGTAGCCCTGGCTATCAGCAGGTGGGCTCCAAGTGTCTCGATGTG  
GATGAGTGTGAGACAGAGGTGTGTCCGGGAGAGAAACAAGCAGTGTGAAAACACCGAGGGC  
GGTTATCGCTGCATCTGTGCCGAGGGCTACAAGCAGATGGAAAGGCATCTGTGTGAAGGAG  
CAGATCCCAGAGTCAGCAGGCTTCTTCTCAGAGATGACAGAAGACGAGTTGGTGGTGCTG  
CAGCAGATGTTCTTTGGCATCATCATCTGTGCACTGGCCACGCTGGCTGCTAAGGGCGAC  
TTGGTGTTCACCGCCATCTTCATTGGGGCTGTGGCGGCCATGACTGGCTACTGGTTGTCA  
GAGCGCAGTGACCGTGTGCTGGAGGGCTTCATCAAGGGCAGATAATCGCGGCCACCACCT  
GTAGGACCTCCTCCCACCCACGCTGCCCCCAGAGCTTGGGCTGCCCTCCTGCTGGACACT  
CAGGACAGCTTGGTTTATTTTTGAGAGTGGGGTAAGCACCCCTACCTGCCTTACAGAGCA  
GCCCAGGTACCCAGGCCCGGGCAGACAAGGCCCTGGGGTAAAAAGTAGCCCTGAAGGTG  
GATACCATGAGCTCTTCACCTGGCGGGGACTGGCAGGCTTCACAATGTGTGAATTTCAA  
AGTTTTTCTTAATGGTGGCTGCTAGAGCTTTGGCCCCCTGCTTAGGATTAGGTGGTCCTC  
ACAGGGGTGGGGCCATCACAGCTCCCTCCTGCCAGCTGCATGCTGCCAGTTCCTGTTCTG  
TGTTACACCATCCCCACCCCCATTGCCACTTATTTATTCATCTCAGGAAATAAAGAAA  
GGTCTTGGAAGTTAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 18**

MAPWPPKGLVPAVLWGLSLFLNLP GPIWLQPSPPPQSSPPPQPHPCHTCRGLVDSFNKGL  
ERTIRDNFGGGNTAWEENLSKYKDSETRLVEVLEGVCSKSDFECHRLLELSEELVESWW  
FHKQQEAPDLFQWLCSDSLKLCCPAGTFGPSCLPCPGGTERPCGGYGQCEGEGTRGSGH  
CDCQAGYGGEACGQCGLGYFEAERNASHLVCSACFGPCARCSGP EESNCLQCKKGWALHH  
LKCVDIDECGTEGANCGADQFCVNTEGSYECRDCAKACLGCMGAGPGRCKKCSPGYQQVG  
SKCLDVDECETEVCPGENKQCENTEGGYRCICAEGYKQMEGICVKEQIPESAGFFSEMTE  
DELVLQQMFFGIIICALATLAAKGLVFTAIFIGAVAAMTGYWLSERSDRVLEGFIKGR

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**FIGURE 19**

GCCCCGGGACTGGCGCAAGGTGCCCAAGCAAGGAAAGAAATAATGAAGAGACACATGTGT  
AGCTGCAGCCTTTTGAACACGCAAGAAGGAAATCAATAGTGTGGACAGGGCTGGAACCT  
TTACCACGCTTGTTGGAGTAGATGAGGAATGGGCTCGTGATTATGCTGACATTCCAGCAT  
GAATCTGGTAGACCTGTGGTTAACCCGTTCCCTCTCCATGTGTCTCCTCCTACAAAGTTT  
TGTTCTTATGATACTGTGCTTTTCATTCTGCCAGTATGTGTCCCAAGGGCTGTCTTTGTTC  
TTCCTCTGGGGGTTTAAATGTACCTGTAGCAATGCAAATCTCAAGGAAATACCTAGAGA  
TCTTCCTCCTGAAACAGTCTTACTGTATCTGGACTCCAATCAGATCACATCTATTCCCAA  
TGAAATTTTAAAGGACCTCCATCAACTGAGAGTTCTCAACCTGTCCAAAATGGCATTGA  
GTTTATCGATGAGCATGCCTTCAAAGGAGTAGCTGAAACCTTGCAGACTCTGGACTTGTC  
CGACAATCGGATTCAAAGTGTGCACAAAAATGCCTTCAATAACCTGAAGGCCAGGGCCAG  
AATTGCCAACAACCCCTGGCACTGCGACTGTACTCTACAGCAAGTTCTGAGGAGCATGGC  
GTCCAATCATGAGACAGCCACAACGTGATCTGTAAAACGTCCGTGTTGGATGAACATGC  
TGGCAGACCATTCTCAATGCTGCCAACGACGCTGACCTTTGTAACCTCCCTAAAAAAC  
TACCGATTATGCCATGCTGGTCACCATGTTTGGCTGGTTCCTATGGTGATCTCATATGT  
GGTATATTATGTGAGGCAAAATCAGGAGGATGCCCGGAGACACCTCGAATACTTGAAATC  
CCTGCCAAGCAGGCAGAAGAAAGCAGATGAACCTGATGATATTAGCACTGTGGTATAGTG  
TCCAAACTGACTGTCATTGAGAAAAGAAAGAAAGTAGTTTGCGATTGCAGTAGAAATAAGT  
GGTTTACTTCTCCCATCCATTGTAAACATTTGAACTTTGTATTTTCAAGTTTTTTTTGAAT  
TATGCCACTGCTGAACTTTTAACAAACACTACAACATAAATAATTTGAGTTTAGGTGATC  
CACCCCTTAATTGTACCCCGATGGTATATTTCTGAGTAAGCTACTATCTGAACATTAGT  
TAGATCCATCTCACATTTTAATAATGAAATTTATTTTTTTAATTTAAAAGCAAATAAAAG  
CTTAACCTTTGAACCATGGGAAAAAAAAAAAAAAAAAAAAAAAAAACA

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**FIGURE 20**

MNLVDLWLTRSLSMCLLLQSFVLMILCFHSASMC PKGCLCSSSGGLNVTCSNANLKEIPR  
DLPPETVLLYLDSNQITSIPNEIFKDLHQLRVNLNLSKNGIEFIDEHAFKGVAETLQTLDL  
SDNRIQSVHKNAFNNL KARARIANNPWHCDCTLQQVLRSMASNHETAHN VICKTSVLDEH  
AGRPFLNAANDADLCNLPKKT TDYAMLVTMFGWFTMVISYV VYYVRQNQEDARRHLEYLK  
SLPSRQKKADEPDDISTVV

**Signal sequence:**

amino acids 1-33

**Transmembrane domain:**

amino acids 205-220

**N-glycosylation site:**

amino acids 47-51, 94-98

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 199-203

**Casein kinase II phosphorylation site:**

amino acids 162-166, 175-179

**N-myristoylation site:**

amino acids 37-43, 45-51, 110-116

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**FIGURE 21**

CGCCACCACTGCGGCCACCGCCAATGAAACGCCTCCCGCTCCTAGTGGTTTTTTTCCACTT  
TGTTGAATTGTTTCCTATACTCAAAATTGCACCAAGACACCTTGTCTCCCAAATGCAAAAT  
GTGAAATACGCAATGGAATTGAAGCCTGCTATTGCAACATGGGATTTTCAGGAAATGGTG  
TCACAATTTGTGAAGATGATAATGAATGTGGAATTTAACTCAGTCCTGTGGCGAAAATG  
CTAATTGCACTAACACAGAAGGAAGTTATTATTGTATGTGTGTACCTGGCTTCAGATCCA  
GCAGTAACCAAGACAGGTTTATCACTAATGATGGAACCGTCTGTATAGAAAATGTGAATG  
CAAAC TGCCATTTAGATAATGTCTGTATAGCTGCAAATATTAATAAAACTTTAACAAAAA  
TCAGATCCATAAAAGAACCTGTGGCTTTGCTACAAGAAGTCTATAGAAATTCTGTGACAG  
ATCTTTCACCAACAGATATAATTACATATATAGAAATATTAGCTGAATCATCTTCATTAC  
TAGGTTACAAGAACAACACTATCTCAGCCAAGGACACCCCTTCTAACTCAACTCTTACTG  
AATTTGTAAAAACCGTGAATAATTTTGTTCAAAGGGATACATTTGTAGTTTGGGACAAGT  
TATCTGTGAATCATAGGAGAACACATCTTACAAAACCTCATGCACACTGTTGAACAAGCTA  
CTTTAAGGATATCCCAGAGCTTCCAAAAGACCACAGAGTTTGATACAAATTCACCGGATA  
TAGCTCTCAAAGTTTTCTTTTTTGATT CATATAACATGAAACATATTCATCCTCATATGA  
ATATGGATGGAGACTACATAAATATATTTCCAAAGAGAAAAGCTGCATATGATTCAAATG  
GCAATGTTGCAGTTGCATTTTTTATATTATAAGAGTATTGGTCCTTTGCTTTCATCATCTG  
ACAACTTCTTATTGAAACCTCAAAATTATGATAATTCTGAAGAGGAGGAAAGAGTCATAT  
CTTCAGTAATTTAGTCTCAATGAGCTCAAACCCACCCACATTATATGAAC TTGAAAAA  
TAACATTTACATTAAGTCATCGAAAGGTCACAGATAGGTATAGGAGTCTATGTGCATTTT  
GGAATTACTCACCTGATACCATGAATGGCAGCTGGTCTTCAGAGGGCTGTGAGCTGACAT  
ACTCAAATGAGACCCACACCTCATGCCGCTGTAATCACCTGACACATTTTGCAATTTTGA  
TGTCCTCTGGTCCTTCCATTGGTATTAAAGATTATAATATTCTTACAAGGATCACTCAAC  
TAGGAATAATTATTTCACTGATTTGTCTTGCCATATGCATTTTTTACCTTCTGGTTCTTCA  
GTGAAATTCAAAGCACCAGGACAACAATTCACAAAAATCTTTGCTGTAGCCTATTTCTTG  
CTGAACTTGTTTTTTCTTGTTGGGATCAATACAAATACTAATAAGCTCTTCTGTTCAATCA  
TTGCCGGA CTGTACACTACTTCTTTTTAGCTGCTTTTGCATGGATGTGCATTGAAGGCA  
TACATCTCTATCTCATTGTTGTGGGTGTCATCTACAACAAGGGATTTTTTGCACAAGAATT  
TTTATATCTTTGGCTATCTAAGCCCAGCCGTGGTAGTTGGATTTTCGGCAGCACTAGGAT  
ACAGATATTATGGCACAACCAAAGTATGTTGGCTTAGCACCGAAAACA ACTTTATTGGA  
GTTTTATAGGACCAGCATGCCTAATCATTCCTTGTTAATCTCTTGGCTTTTGGAGTCATCA  
TATACAAAGTTTTTTCGTACACTGCAGGGTTGAAACCAGAAGTTAGTTGCTTTGAGAAACA  
TAAGGTCTTGTCAGAGAGGCCCTCGCTCTTCTGTTCCCTTCTCGGCACCACCTGGATCT  
TTGGGGTTCTCCATGTTGTGCACGCATCAGTGGTTACAGCTTACCTCTTCACAGTCAGCA  
ATGCTTTCCAGGGGATGTTTCATTTTTTTTATTCTGTGTGTTTTATCTAGAAAGATTCAAG  
AAGAATATTACAGATTGTTCAAAAATGTCCCCTGTTGTTTTGGATGTTTAAGGTAAACAT  
AGAGAATGGTGGATAATTACAAC TGCAAAAAATAAAAATTCCAAGCTGTGGATGACCAA  
TGTATAAAAATGACTCATCAAATTATCCAATTATTA ACTACTAGACAAAAAGTATTTTAA  
ATCAGTTTTTCTGTTTATGCTATAGGAACTGTAGATAATAAGGTAAAATTATGTATCATA  
TAGATATACTATGTTTTTCTATGTGAAATAGTTCTGTCAAAAATAGTATTGCAGATATTT  
GGAAAGTAATTGGTTTTCTCAGGAGTGATATCACTGCACCCAAGGAAAGATTTTCTTTCTA  
ACACGAGAAGTATATGAATGTCCTGAAGGAAACCACTGGCTTGATATTTCTGTGACTCGT  
GTTGCCTTTGAACTAGTCCCCTACCACTCGGTAATGAGCTCCATTACAGAAAGTGGAA  
CATAAGAGAATGAAGGGGCAGAATATCAAACAGTGAAAAGGGAATGATAAGATGTATTTT  
GAATGAACTGTTTTTTCTGTAGACTAGCTGAGAAATTGTTGACATAAAATAAAGAATTGA  
AGAAACACATTTTACCATTTTGTGAATTGTTCTGAACTTAAATGTCCACTAAAACAACCTT  
AGACTTCTGTTTGCTAAATCTGTTTCTTTTTCTAATATTCTAAAAA AAAAAAAGGTTT  
ACCTCCACAAATTGAAA

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**FIGURE 22**

MKRLPLLVFSTLLNCSYTQNCTKTPCLPNAKCEIRNGIEACYCNMGFSGNGVTICEDDN  
ECGNLTQSCGENANCTNTEGSYYCMCVPGFRSSSNQDRFITNDGTVCIENVNANCHLDNV  
CIAANINKTLTKIRSIKEPVALLQEVYRNSVTDLSPTDIITYIEILAESSLLGYKNNTI  
SAKDTLSNSTLTEFVKTVNNFVQRDTFVVWDKLSVNHRRTHLTCLMHTVEQATLRISQSF  
QKTTEFDTNSTDIALKVFFFDSDYNMKHIHPHMNDGDYINIFPKRKAAYDSNGNVAVAF  
YYKSIGPLLSSSDNFLKLPQNYDNSEEEERVISSVISVSMSSNPPTLYELEKITFTLSHR  
KVTDRYRSLCAFWNYSPTMNGSWSSEGCETYSNETHTSCRCNHLTHFAILMSSGPSIG  
IKDYNILTRITQLGIIISLICLAICIFTFWFFSEIQSTRTTIHKNLCCSLFLAELVFLVG  
INTNTNKLFCSSIAGLLHYFFLAFAWMCIEGIHLYLIVVGVIYNKGFLHKNFYIFGYLS  
PAVVVGFSALGYRYYGTTKVCWLSTENNFIWSFIGPACLIILVNLLAFGVIIYKVRHT  
AGLKPEVSCFENIRSCARGALALLFLLGTTWIFGVLHVHASVVTAYLFTVSNAFQGMFI  
FLFLCVLSRKIQEYYRLFKNPCCFGCLR

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**FIGURE 23**

CTCCTCTTAACATACTTGCAGCTAAAACTAAATATTGCTGCTTGGGGACCTCCTTCTAGC  
CTTAAATTTTCTAGCTCATCACCTTCACCTGCCTTGGTTCATGGCTCTGCTATTCTCCTTGAT  
CCTTGCCATTTTGCACCAGACCTGGATTCTAGCGTCTCCATCTGGAGTGCGGCTGGTGGG  
GGGCTCCACCGCTGTGAAGGGCGGGTGGAGGTGGAACAGAAAGGCCAGTGGGGCACCGT  
GTGTGATGACGGCTGGGACATTAAGGACGTGGCTGTGTTGTGCCGGGAGCTGGGCTGTGG  
AGCTGCCAGCGGAACCCCTAGTGGTATTTTGTATGAGCCACCAGCAGAAAAAGAGCAAAA  
GGTCTCATCCAATCAGTCAGTTGCACAGGAACAGAAGATACATTGGCTCAGTGTGAGCA  
AGAAGAAGTTTATGATTGTTTACATGATGAAGATGCTGGGGCATCGTGTGAGAACCAGA  
GAGCTCTTTCTCCCCAGTCCCAGAGGGTGTGAGGCTGGCTGACGGCCCTGGGCATTGCAA  
GGGACGCGTGGAAGTGAAGCACCAGAACAGTGGTATACCGTGTGCCAGACAGGCTGGAG  
CCTCCGGGGCCGCAAAGGTGGTGTGCCGGCAGCTGGGATGTGGGAGGGCTGTACTGACTCA  
AAAACGCTGCAACAAGCATGCCTATGGCCGAAAACCCATCTGGCTGAGCCAGATGTCTATG  
CTCAGGACGAGAAGCAACCCTTCAGGATTGCCCTTCTGGGCCTTGGGGGAAGAACACCTG  
CAACCATGATGAAGACACGTGGGTCTGAATGTGAAGATCCCTTTGACTTGAGACTAGTAGG  
AGGAGACAACCTCTGCTCTGGGCGACTGGAGGTGCTGCACAAGGGCGTATGGGGCTCTGT  
CTGTGATGACAACTGGGGAGAAAAGGAGGACCAGGTGGTATGCAAGCAACTGGGCTGTGG  
GAAGTCCCTCTCTCCCTCCTTCAGAGACCGGAAATGCTATGGCCCTGGGGTTGGCCGCAT  
CTGGCTGGATAATGTTTCGTTGCTCAGGGGAGGAGCAGTCCCTGGAGCAGTGCCAGCACAG  
ATTTTGGGGGTTTCACGACTGCACCCACCAGGAAGATGTGGCTGTCTATCTGCTCAGTGTA  
GGTGGGCATCATCTAATCTGTTGAGTGCCTGAATAGAAGAAAAACACAGAAGAAGGGAGC  
ATTTACTGTCTACATGACTGCATGGGATGAACACTGATCTTCTTCTGCCCTTGGACTGGG  
ACTTATACTTGGTGCCCTGATTCTCAGGCCTTCAGAGTTGGATCAGAAGTTACAACATC  
AGGTCTAGTTCTCAGGCCATCAGACATAGTTTGGAACTACATCACCACCTTTTCTATGTC  
TCCACATTGCACACAGCAGATTCCCAGCCTCCATAATTGTGTGTATCAACTACTTAAATA  
CATTCTCATACACCATTTGTCC  
TGTTTCTCTGAAGAACTCTGACAAAATACAGATTTTGGTACTGAAAGAGATTCTAGAGGA  
ACGGAATTTTAAGGATAAATTTTCTGAATTGGTTATGGGGTTTCTGAAATTGGCTCTATA  
ATCTAATTAGATATAAAATTCTGGTAACTTTATTTACAATAATAAAGATAGCACTATGTG  
TTCAAA



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**FIGURE 24**

MALLFSLILAICTRPGFLASPSGVRLVGGLHRCEGRVEVEQKGQWGTVCDDGWDIKDVAV  
LCRELGCGAASGTPSGILYEPPAEKEQKVLIQSVSCTGTEDTLAQCEQEVEYDCSHDEDA  
GASCENPESSFSVPPEGVRLADGPGHCKGRVEVKHQNQWYTVQCQTGWSLRAAKVVCRQLG  
CGRAVLTQKRCNKHAYGRKPIWLSQMSCSGREATLQDCPSGPWGKNTCNHDEDTWVECED  
PFDLRLVGGDNLCSGRLEVLHKGWVGSVCDDNWGEKEDQVVCKQLGCGKSLSPSFRDRKC  
YGPVGRIWLDNVRCSGEEQSLEQCQHRFWGFHDCTHQEDVAVICSV

**Signal sequence:**

amino acids 1-15

**Casein kinase II phosphorylation site:**amino acids 47-51, 97-101, 115-119, 209-213, 214-218, 234-238,  
267-271, 294-298, 316-320, 336-340**N-myristoylation site:**amino acids 29-35, 43-49, 66-72, 68-74, 72-78, 98-104, 137-143,  
180-186, 263-269, 286-292**Amidation site:**

amino acids 196-200

**Speract receptor repeated domain signature:**

amino acids 29-67, 249-287

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**FIGURE 25**

CGGACGCGTG GGGCGTCCGGCGGTGCGAGAGCCAGGAGGCGGAGGCGCGGGGCCAGCCTG  
GGCCCCAGCCCACACCTTCACCAGGGCCCAGGAGCCACCATGTGGCGATGTCCACTGGGG  
CTACTGCTGTTGCTGCCGCTGGCTGGCCACTTGGCTCTGGGTGCCCAGCAGGGTCGTGGG  
CGCCGGGAGCTAGCACCGGGTCTGCACCTGCCGGGCATCCGGGACGCGGGAGGCCGGTAC  
TGCCAGGAGCAGGACCTGTGCTGCCGCGGGCCGTGCCGACGACTGTGCCCTGCCCTACCTG  
GGCGCCATCTGTTACTGTGACCTCTTCTGCAACCGCACGGTCTCCGACTGCTGCCCTGAC  
TTCTGGGACTTCTGCCTCGGCGTGCCACCCCTTTTCCCCCGATCCAAGGATGTATGCAT  
GGAGGTCGTATCTATCCAGTCTTGGGAACGTACTGGGACAACGTGAACCGTTGCACCTGC  
CAGGAGAACAGGCAGTGGCATGGTGGATCCAGACATGATCAAAGCCATCAACCAGGGCAA  
CTATGGCTGGCAGGCTGGGAACCACAGCGCCTTCTGGGGCATGACCCTGGATGAGGGCAT  
TCGCTACCGCTGGGCACCATCCGCCATCTTCCTCGGTCATGAACATGCATGAAATTTA  
TACAGTGCTGAACCCAGGGGAGGTGCTTCCCACAGCCTTCGAGGCCTCTGAGAAGTGGCC  
CAACCTGATTCATGAGCCTCTTGACCAAGGCAACTGTGCAGGCTCCTGGGCCTTCTCCAC  
AGCAGCTGTGGCATCCGATCGTGTCTCAATCCATTCTCTGGGACACATGACGCCTGTCT  
GTCGCCCCAGAACCTGCTGTCTTGACACCCACCAGCAGCAGGGCTGCCGCGGTGGGCG  
TCTCGATGGTGCTGCTGGTGGTTCCTGCGTCGCCGAGGGGTGGTGTCTGACCACTGCTACCC  
CTTCTCGGGCCGTGAACGAGACGAGGCTGGCCCTGCCGCCCCCTGTATGATGCACAGCCG  
AGCCATGGGTGCGGGCAAGCGCCAGGCCACTGCCCACTGCCCAACAGCTATGTTAATAA  
CAATGACATCTACCAGGTCATCCTGTCTACCGCCTCGGCTCCAACGACAAGGAGATCAT  
GAAGGAGCTGATGGAGAATGGCCCTGTCCAAGCCCTCATGGAGGTGCATGAGGACTTCTT  
CCTATAACAAGGAGGCATCTACAGCCACACGCCAGTGAGCCTTGGGAGGCCAGAGAGATA  
CCGCCGGCATGGGACCCACTCAGTCAAGATCACAGGATGGGGAGAGGAGACGCTGCCAGA  
TGGAAGGACGCTCAAATACTGGACTGCGGCCAACTCCTGGGGCCCAGCCTGGGGCGAGAG  
GGGCCACTTCCGCATCGTGCGCGGCGTCAATGAGTGCGACATCGAGAGCTTCGTGCTGGG  
CGTCTGGGGCCGCGTGGGCATGGAGGACATGGGTCACTGAGGCTGCGGGCACCACGC  
GGGGTCCGGCCTGGGATCCAGGCTAAGGGCCGGCGGAAGAGGCCCAATGGGGCGGTGAC  
CCCAGCCTCGCCCGACAGAGCCCGGGCGCAGGCGGGCGCCAGGGCGCTAATCCCGGCGC  
GGGTTCGCTGACGCGAGCGCCCCGCTGGGAGCCGCGGGCAGGCGAGACTGGCGGAGCCC  
CCAGACCTCCCAGTGGGGACGGGGCAGGGCCTGGCCTGGGAAGAGCACAGCTGCAGATCC  
CAGGCCTCTGGCGCCCCCACTCAAGACTACCAAAGCCAGGACACCTCAAGTCTCCAGCCC  
CAATACCCACCCCAATCCCGTATTCTTTTTTTTTTTTTTTTTTTAGACAGGGTCTTGCTCCG  
TTGCCAGGTTGGAGTGCAGTGGCCCATCAGGGCTCACTGTAACCTCCGACTCCTGGGTT  
CAAGTGACCCTCCACCTCAGCCTCTCAAGTAGCTGGGACTACAGGTGCACCACCACACC  
TGGCTAATTTTTGTATTTTTTGTAAAGAGGGGGTCTCACTGTGTTGCCCAGGCTGGTTT  
CGAACTCCTGGGCTCAAGCGGTCCACCTGCCTCCGCCTCCCAAAGTGCTGGGATTGCAGG  
CATGAGCCACTGCACCCAGCCCTGTATTCTTATTCTTCAGATATTATTTTTCTTTTAC  
TGTTTTAAATAAAACCAAAGTATTGATAAAAAAAA

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**FIGURE 26**

MWRCPLGLLLLLPLAGHLALGAQQGRGRRELAPGLHLRGIRDAGGRYCQEQLCCRGRAD  
DCALPYLGAIICYCDLFCNRTVSDCCPDFWDFCLGVPPFPPIQGCMHGGRIYPVLGTYWD  
NCNRCTCQENRQWHGGSRHDQSHQPGQLWLAGWEPQRLLGHDPG

**N-glycosylation site:**

amino acids 78-82, 161-165

**Casein kinase II phosphorylation site:**

amino acids 80-84, 117-121, 126-130, 169-173, 205-209, 296-300,  
411-415

**N-myristoylation site:**

amino acids 21-27, 39-45, 44-50, 104-110, 160-164, 224-230,  
269-275, 378-384, 442-448

**Amidation site:**

amino acids 26-30, 318-322

**Eukaryotic thiol (cysteine) proteases histidine active site:**

amino acids 398-409

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**FIGURE 27**

CCCACGCGTCCGGCAGGTTTTCTTCAAGCCAAGAAGGACACGGATTGGCTGAAGGAGAA  
AGTGCAGAGCTTGCAGACACTGGCTGCCAACAACCTCTGCGTTGGCCAAAGCCAACAACGA  
CACCTTGGAGGATATGAACAGCCAGCTCAACTCATTACAGGTCAGATGGAGAACATCAC  
CACTATCTCTCAAGCCAACGAGCAGAACCTGAAAGACCTGCAGGACTTACACAAAGATGC  
AGAGAATAGAACAGCCATCAAGTTCAACCAACTGGAGGAACGCTTCCAGCTCTTTGAGAC  
GGATATTGTGAACATCATTAGCAATATCAGTTACACAGCCCACCACCTGCGGACGCTGAC  
CAGCAATCTAAATGAAGTCAGGACCACTTGCACAGATACCTTACCAAACACACAGATGAT  
CTGACCTCCTTGAATAATACCCTGGCCAACATCCGTTTGGATTCTGTTTCTCTCAGGATG  
CAACAAGATTTGATGAGGTCGAGGTTAGACACTGAAGTAGCCAACCTTATCAGTGATTATG  
GAAGAAATGAAGCTAGTAGACTCCAAGCATGGTCAGCTCATCAAGAATTTTACAATACTA  
CAAGGTCCACCGGGCCCCAGGGGTCCAAGAGGTGACAGAGGATCCCAGGGACCCCCTGGC  
CCAAGTGGCAACAAGGGACAGAAAGGAGAGAAGGGGGAGCCTGGACCACCTGGCCCTGCG  
GGTGAGAGAGGCCCAATTGGACCAGCTGGTCCCCCGGAGAGCGTGGCGGCAAAGGATCT  
AAAGGCTCCCAGGGCCCCAAAGGCTCCCGTGGTTCCCCTGGGAAGCCCGGCCCTCAGGGC  
CCCAGTGGGGACCCAGGCCCCCCGGGGCCACCAGGCAAAGAGGGACTCCCCGGCCCTCAG  
GGCCCTCCTGGCTTCCAGGGACTTCAGGGCACCGTTGGGGAGCCTGGGGTGCCTGGACCT  
CGGGGACTGCCAGGCTTGCTGGGGTACCAGGCATGCCAGGCCCAAGGGCCCCCCCCGGC  
CCTCCTGGCCCATCAGGAGCGGTGGTGGCCCTGGCCCTGCAGAATGAGCCAACCCCGGCA  
CCGGAGGACAATAGCTGCCCGCCTCACTGGAAGAACTTCACAGACAAATGCTACTATTTT  
TCAGTTGAGAAAGAAATTTTTGAGGATGCAAAGCTTTTCTGTGAAGACAAGTCTTCACAT  
CTTGTTTTTCATAAACACTAGAGAGGAACAGCAATGGATAAAAAAACAGATGGTAGGGAGA  
GAGAGCCACTGGATCGGCCTCACAGACTCAGAGCGTGAAAATGAATGGAAGTGGCTGGAT  
GGGACATCTCCAGACTACAAAAATTGGAAAGCTGGACAGCCGGATAACTGGGGTCATGGC  
CATGGGCCAGGAGAAGACTGTGCTGGGTTGATTTATGCTGGGCAGTGGAACGATTTCCAA  
TGTGAAGACGTCAATAACTTCATTTGCGAAAAAGACAGGGAGACAGTACTGTCATCTGCA  
TTATAACGGACTGTGATGGGATCACATGAGCAAATTTTCAGCTCTCAAAGGCAAAGGACA  
CTCCTTTCTAATTGCATCACCTTCTCATCAGATTGAAAAAAAAAAAAAGCACTGAAAACCAA  
TTACTGAAAAAAAAAATTGACAGCTAGTGTTTTTTTACCATCCGTCATTACCCAAAGACTTGG  
GAACTAAATGTTCCCCAGGGTGATATGCTGATTTTCATTGTGCACATGGACTGAATCAC  
ATAGATTCTCCTCCGTGAGTAACCGTGCGATTATACAAATTATGTCTTCCAAAGTATGGA  
ACACTCCAATCAGAAAAAGGTTATCATTGGTCGTTGAGTTATGGGAAGAACTTAAGCATA  
TACTGTGTAAACAGTGCCATACATTTCTAAAATCCCAAGTGTAGGAAAAATATGCAGACA  
TACAGATATATAGGCCAACTATTAGTAATAATATGAAATATACTTAAAGAGCTTTTAAAA  
CTTTGTATTTTTGTACAAAAAAA

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**FIGURE 28**

MQQDLMRSRLDTEVANLSVIMEEMKLVD SKHGQLIKNFTILQGPPGPRGPRGDRGSQGPP  
GPTGNKGQKGEKGEPGPPGPAGERGP IGPAGPPGERGGKGSKGSQGPKGSRGSPGKPGPQ  
GPSGDPGPPGPPGKEGLPGPQGPPGFQGLQGT VGE PGVP GPRGLPGLPGVP GMPGPKGPP  
GPPGPSGAVVPLALQNEPTPAPEDNSCP PHWKNF TDKCY YFSVEKEIFEDAKLFCEDKSS  
HLVFINTREEQQWIKKQMVGRE SHWIGLTD SERENEWK WLDGTSPDYKNWKAGQPDN WGH  
GHGPGEDCAGLIYAGQW NDFQCEDVNNFICEKDRETVLSSAL

**Signal sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

16-19, 37-40, 213-216

**Tyrosine kinase phosphorylation site:**

212-220

**N-myristoylation site:**

97-102, 100-105, 148-153, 267-272, 293-298, 310-315

**Cell attachment sequence:**

51-53

**C-type lectin domain signature:**

308-330

**Lectin C-type domain:**

233-330

**Collagen triple helix repeat:**

43-102, 127-186

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**FIGURE 29**

GGACTAATCTGTGGGAGCAGTTTATTCCAGTATCACCCAGGGTGCAGCCACACCAGGACT  
GTGTTGAAGGGTGTGTTTTTTTCTTTTAAATGTAATACCTCCTCATCTTTTCTTCTTACAC  
AGTGTCTGAGAACATTTACATTATAGATAAGTAGTACATGGTGGATAACTTCTACTTTTA  
GGAGGACTACTCTCTTCTGACAGTCCTAGACTGGTCTTCTACACTAAGACACCCATGAAGG  
AGTATGTGCTCCTATTATTCTGGCTTTGTGCTCTGCCAAACCCCTTCTTTAGCCCTTCAC  
ACATCGCACTGAAGAATATGATGCTGAAGGATATGGAAGACACAGATGATGATGATGATG  
ATGATGATGATGATGATGATGATGAGGACAACCTCTCTTTTCCAACAAGAGAGCCAAGAA  
GCCATTTTTTTTCCATTTGATCTGTTTCCAATGTGTCCATTTGGATGTCAGTGCTATTTCAC  
GAGTTGTACATTGCTCAGATTTAGGTTTGACCTCAGTCCCAACCAACATTCCATTTGATA  
CTCGAATGCTTGATCTTCAAAACAATAAAATTAAGGAAATCAAAGAAAATGATTTTAAAG  
GACTCACTTCACTTTATGGTCTGATCCTGAACAACAACAAGCTAACGAAGATTACCCAA  
AAGCCTTTCTAACCACAAAGAAGTTGCGAAGGCTGTATCTGTCCCACAATCAACTAAGTG  
AAATACCACTTAATCTTCCCAAATCATTAGCAGAACTCAGAATTCATGAAAATAAAGTTA  
AGAAAATACAAAAGGACACATTCAAAGGAATGAATGCTTTACACGTTTTGGAAATGAGTG  
CAAACCCCTCTTGATAATAATGGGATAGAGCCAGGGGCATTTGAAGGGGTGACGGTGTTCC  
ATATCAGAATTGCAGAAGCAAACTGACCTCAGTTCCTAAAGGCTTACCACCAACTTTAT  
TGGAGCTTCACTTAGATTATAATAAAATTTCAACAGTGGAACCTTGAGGATTTTAAACGAT  
ACAAAGAACTACAAAGGCTGGGCCTAGGAAACAACAAATCACAGATATCGAAAATGGGA  
GTCTTGCTAACATAACCACGTGTGAGAGAAATACATTTGGAAAACAATAAACTAAAAA  
TCCCTTCAGGATTACCAGAGTTGAAATACCTCCAGATAATCTTCCTTCATTCTAATTCAA  
TTGCAAGAGTGGGAGTAAATGACTTCTGTCCAACAGTGCCAAAGATGAAGAAATCTTTAT  
ACAGTGCAATAAGTTTATTCAACAACCCGGTGAAATACTGGGAAATGCAACCTGCAACAT  
TTCGTTGTGTTTTGAGCAGAATGAGTGTTGAGCTTGGGAACTTTGGAATGTAATAATTAG  
TAATTGGTAATGTCCATTTAATATAAGATTCAAAAATCCCTACATTTGGAATACTTGAAC  
TCTATTAATAATGGTAGTATTATATATACAAGCAAATATCTATTCTCAAGTGGAAGTCC  
ACTGACTTATTTTATGACAAGAAATTTCAACGGAATTTTGCCAAACTATTGATACATAAG  
GGGTTGAGAGAAACAAGCATCTATTGCAGTTTCTTTTTTGCCTACAAATGATCTTACATA  
AATCTCATGCTTGACCATTCCTTTCTTCATAACAAAAAGTAAGATATTCGGTATTTAAC  
ACTTTGTTATCAAGCACATTTTAAAAAGAACTGTACTGTAAATGGAATGCTTGACTTAGC  
AAAATTTGTGCTCTTTTCATTTGCTGTTAGAAAAACAGAATTAACAAAGACAGTAATGTGA  
AGAGTGCAATTACACTATTCTTATTCTTTAGTAACTTGGGTAGTACTGTAATATTTTTAAT  
CATCTTAAAGTATGATTTGATATAATCTTATTGAAATTACCTTATCATGTCTTAGAGCCC  
GTCTTTATGTTTAAACTAATTTCTTAAATAAAGCCTTCAGTAAATGTTTATTACCAAC  
TTGATAAATGCTACTCATAAGAGCTGGTTTGGGGCTATAGCATATGCTTTTTTTTTTTTA  
ATTATTACCTGATTTAAAAATCTCTGTAAAAACGTGTAGTGTTTCATAAAATCTGTAAC  
CGCATTTTAATGATCCGCTATTATAAGCTTTTAATAGCATGAAAATTGTTAGGCTATATA  
ACATTGCCACTTCAACTCTAAGGAATATTTTTGAGATATCCCTTTGGAAGACCTTGCTTG  
GAAGAGCCTGGACACTAACAATCTACACCAAATTTGTCTCTTCAAATACGTATGGACTGG  
ATAACTCTGAGAAACACATCTAGTATAACTGAATAAGCAGAGCATCAAATTAAACAGACA  
GAAACCGAAAGCTCTATATAAATGCTCAGAGTTCTTTATGTATTTCTTATTGGCATTCAA  
CATATGTAAATCAGAAAACAGGGAAATTTTCATTAAAAATATTGGTTTGAAAT

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**FIGURE 30**

MKEYVLLLFLALCSAKPFFSPSHIALKNMMLKDMEDTDDDDDDDDDDDDDEDNSLFPTRE  
PRSHFFPFDLFPMPFCQCYSRVVHCSDLGLTSVPTNIPFDTRMLDLQNNKIKEIKEND  
FKGLTSLYGLIILNNKLTKIHPKAFLTTKLRRLYLSHNQLSEIPLNLPKSLAELRIHEN  
KVKKIQKDTFKGMNALHVLEMSANPLDNNGIEPGAEGVTVFHIRIAEAKLTSVPKGLPP  
TLLELHLDYNKISTVELEDFKRYKELQRLGLGNNKITDIENGLANIPRVREIHLENNKL  
KKIPSGLPKYLQIIFLHSNSIARVGVNDFCPTVPKMKKSLYSAISLFNNPVKYWEMQP  
ATFRCVLSRMSVQLGNFGM

**Signal sequence:**  
amino acids 1-15

**N-glycosylation site:**  
amino acids 281-285

**N-myristoylation sites:**  
amino acids 129-135, 210-216, 214-220, 237-243, 270-276,  
282-288

**Leucine zipper pattern:**  
amino acids 154-176

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**FIGURE 31**

AGCAGGGAAATCCGGATGTCTCGGTTATGAAGTGGAGCAGTGAGTGTGAGCCTCAACATA  
GTTCCAGAACTCTCCATCCGGACTAGTTATTGAGCATCTGCCTCTCATATCACCAGTGGC  
CATCTGAGGTGTTTTCCCTGGCTCTGAAGGGGTAGGCACGATGGCCAGGTGCTTCAGCCTG  
GTGTTGCTTCTCACTTCCATCTGGACCACGAGGCTCCTGGTCCAAGGCTCTTTGCGTGCA  
GAAGAGCTTTCCATCCAGGTGTCTATGCAGAATTATGGGGATCACCTTGTGAGCAAAAAG  
GCGAACCAGCAGCTGAATTTACAGAAGCTAAGGAGGCCTGTAGGCTGCTGGGACTAAGT  
TTGGCCGGCAAGGACCAAGTTGAAACAGCCTTGAAAGCTAGCTTTGAAACTTGCAGCTAT  
GGCTGGGTTGGAGATGGATTTCGTGGTTCATCTCTAGGATTAGCCCAAACCCCAAGTGTGGG  
AAAAATGGGGTGGGTGTCTGATTGGAAGGTTCCAGTGAGCCGACAGTTTGCAGCCTAT  
TGTTACAACCTCATCTGATACTTGGACTAACTCGTGCATTCCAGAAATTATCACCACCAA  
GATCCCATATTCAACACTCAAACGCAACACAAACAGAAATTTATTGTGAGTGACAGT  
ACCTACTCGGTGGCATCCCCTTACTCTACAATACCTGCCCCCTACTACTCTCCTCTGCT  
CCAGCTTCCACTTCTATTCCACGGAGAAAAAATTGATTTGTGTACAGAAAGTTTTTATG  
GAACTAGCACCATGTCTACAGAACTGAACCATTTGTTGAAAATAAAGCAGCATTCAAG  
AATGAAGCTGCTGGGTTTGGAGGTGTCCCCACGGCTCTGCTAGTGCTTGTCTCCTCTTC  
TTTGGTGCTGCAGCTGGTCTTGGATTTTGCTATGTCAAAGGTATGTGAAGGCCTTCCCT  
TTTACAAACAAGAATCAGCAGAAGGAAATGATCGAAACCAAAGTAGTAAAGGAGGAGAAG  
GCCAATGATAGCAACCCTAATGAGGAATCAAAGAAAACCTGATAAAAACCCAGAAGAGTCC  
AAGAGTCCAAGCAAACTACCGTGCGATGCCTGGAAGCTGAAGTTTAGATGAGACAGAAA  
TGAGGAGACACACCTGAGGCTGGTTTTCTTTTCATGCTCCTTACCCTGCCCCAGCTGGGGAA  
ATCAAAAGGGCCAAAGAACCAGAAAGAAAGTCCACCCTTGGTTCCCTAACTGGAATCAGC  
TCAGGACTGCCATTGGACTATGGAGTGCACCAAGAGAATGCCCTTCTCCTTATTGTAAC  
CCTGTCTGGATCCTATCCTCCTACCTCCAAAGCTTCCACGGCCTTTCTAGCCTGGCTAT  
GTCCTAATAATATCCCACTGGGAGAAAGGAGTTTTGCAAAGTGCAAGGACCTAAACATC  
TCATCAGTATCCAGTGGTAAAGGCTCCTGGCTGTCTGAGGCTAGGTGGGTTGAAAGC  
CAAGGAGTCACTGAGACCAAGGCTTTCTCTACTGATTCCGCAGCTCAGACCCCTTTCTTCA  
GCTCTGAAAGAGAAACACGTATCCACCTGACATGTCTTCTGAGCCCGGTAAGAGCAAA  
AGAATGGCAGAAAAGTTTAGCCCCTGAAAGCCATGGAGATTCTCATAACTTGAGACCTAA  
TCTCTGTAAAGCTAAAATAAAGAAATAGAACAAGGCTGAGGATACGACAGTACACTGTCA  
GCAGGGACTGTAAACACAGACAGGGTCAAAGTGTCTTCTCTGAACACATTGAGTTGGAAT  
CACTGTTTAGAACACACACACTTACTTTTTCTGGTCTCTACCACTGCTGATATTTTCTCT  
AGGAAATATACTTTTACAAGTAACAAAAATAAAAACTCTTATAAATTTCTATTTTTATCT  
GAGTTACAGAAATGATTACTAAGGAAGATTACTCAGTAATTTGTTTAAAAAGTAATAAAA  
TTCAACAAACATTTGCTGAATAGCTACTATATGTCAAGTGCTGTGCAAGGTATTACACTC  
TGTAATTGAATATTATTCTCAAAAAATTGCACATAGTAGAACGCTATCTGGGAAGCTAT  
TTTTTTCAGTTTTGATATTTCTAGCTTATCTACTTCCAACTAATTTTTATTTTTGCTGA  
GACTAATCTTATTCATTTTCTCTAATATGGCAACCATTATAACCTTAATTTATTATTAAC  
ATACCTAAGAAGTACATTGTTACCTCTATATACCAAAGCACATTTTAAAAGTGCCATTAA  
CAAATGTATCACTAGCCCTCCTTTTTTCCAACAAGAAGGGACTGAGAGATGCAGAAATATT  
TGTGACAAAAAATTAAAGCATTTAGAAAACCTT



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**FIGURE 32**

MARCFSLVLLLLTSIWTTTRLLVQGSLRAEELSIQVSCRIMGITLVSKKANQQQLNFTEAKEA  
CRLGLSLAGKDQVETALKASFETCSYGWVGDFVVISRISPNPKCGKNGVGVLIWKVPV  
SRQFAAYCYNSSDTWTNSCIPEIITTKDPIFNTQTATQTTEFIVSDSTYSVASPYSTIPA  
PTTTPPAPASTSIPRRKKLICVTEVFMETSTMSTETEPFVENKAAFKNEAAGFGGVPTAL  
LVLALLFFGAAAGLGFCYVKRYVKAFPFTNKNQQKEMIETKVVKEEKANDSNPNEESKKT  
DKNPEESKSPSKTTVRCLEAEV

**Signal sequence:**  
amino acids 1-16

**Transmembrane domain:**  
amino acids 235-254

**N-glycosylation site:**  
amino acids 53-57, 130-134, 289-293

**Casein kinase II phosphorylation site:**  
amino acids 145-149, 214-218

**Tyrosine kinase phosphorylation site:**  
amino acids 79-88

**N-myristoylation site:**  
amino acids 23-29, 65-71, 234-240, 235-239, 249-255, 253-259

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### FIGURE 33

[illegible]

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TCTACTTATGTTGGACACTTGGCAGAAGGACCGTGCCCGGCGGCCTCATTTTGACCAGCT  
GGTGGCTGCATTTGACAAGATGATCCGCAAGCCAGATACCCTGCAGGCTGGCGGGGACCC  
AGGGGAAAGGCCTTCCCAGGCCCTTCTGACCCCTGTGGCCCTGGACTTTCCTTGTCTGGA  
CTCACCCCAGGCCTGGCTTTCAGCCATTGGACTGGAGTGCTACCAGGACAACCTTCTCCAA  
GTTTGGCCTCTGTACCTTCAGTGATGTGGCTCAGCTCAGCCTAGAAGACCTGCCTGCCCT  
GGGCATCACCTTGGCTGGCCACCAGAAGAAGCTGCTGCACCACATCCAGCTCCTTCAGCA  
ACACCTGAGGCAGCAGGGCTCAGTGGAGGTCTGAGAATGACGATACCCGTGACTCAGCCC  
TGGACACTGGTCCGAGAAGGGACATGTGGGACGTGAGCCGGGCTCCAACAGCCTCTGTGA  
GAGATGCCCCACACCAAACCCAACCCTCCGATGGCTGCATTCCCTGGTCCTCCGCTTTTC  
CACCAGCCCCCTCCTCATTAAGGGAAAGAAGGGAATTTGCAAAAAAAAAAAAAAAAAAAAA  
AAAAAA

FIGURE 34

Amino acids 310-313;399-402

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**FIGURE 35**

GGGGTCTCCCTCAGGGCCGGGAGGCACAGCGGTCCCTGCTTGCTGAAGGGCTGGATGTAC  
GCATCCGCAGGTTCCCGCGGACTTGGGGGCGCCCGCTGAGCCCCGGCGCCCGCAGAAGAC  
TTGTGTTTGCCTCCTGCAGCCTCAACCCGGAGGGCAGCGAGGGCCTACCACCATGATCAC  
TGGTGTGTTTCTGAGCATGCGCTTGTGGACCCAGTGGGCGTCCTGACCTCGCTGGCGTACTG  
CCTGCACCAGCGGCGGGTGGCCCTGGCCGAGCTGCAGGAGGCGGATGGCCAGTGTCCGGT  
CGACCGCAGCCTGCTGAAGTTGAAAATGGTGCAGGTTCGTGTTTCGACACGGGGCTCGGAG  
TCCTCTCAAGCCGCTCCCGCTGGAGGAGCAGGTAGAGTGGAACCCCCAGCTATTAGAGGT  
CCCACCCCAAACCTCAGTTTGATTACACAGTCACCAATCTAGCTGGTGGTCCGAAACCATA  
TTCTCCTTACGACTCTCAATACCATGAGACCACCCTGAAGGGGGGCATGTTTGCTGGGCA  
GCTGACCAAGGTGGGCATGCAGCAAATGTTTGCCTTGGGAGAGAGACTGAGGAAGAACTA  
TGTGGAAGACATTCCCTTTCTTTCACCAACCTTCAACCCACAGGAGGTCTTTATTTCGTTT  
CACTAACATTTTTTCGGAATCTGGAGTCCACCCGTTGTTTGCTGGCTGGGCTTTTCCAGTG  
TCAGAAAGAAGGACCCATCATCATCCACACTGATGAAGCAGATTTCAGAAGTCTTGTATCC  
CAACTACCAAAGCTGCTGGAGCCTGAGGCAGAGAACCAGAGGCCGAGGCAGACTGCCTC  
TTTACAGCCAGGAATCTCAGAGGATTTGAAAAGGTGAAGGACAGGATGGGCATTGACAG  
TAGTGATAAAGTGGACTTCTTCATCCTCCTGGACAACGTGGCTGCCGAGCAGGCACACAA  
CCTCCCAAGCTGCCCCATGCTGAAGAGATTTGCACGGATGATCGAACAGAGAGCTGTGGA  
CACATCCTTGTACATACTGCCCAAGGAAGACAGGGAAAGTCTTCAGATGGCAGTAGGCCC  
ATTCTCCACATCCTAGAGAGCAACCTGCTGAAAGCCATGGACTCTGCCACTGCCCCCGA  
CAAGATCAGAAAGCTGTATCTCTATGCGGCTCATGATGTGACCTTCATACCGCTCTTAAT  
GACCCTGGGGATTTTTGACCACAAATGGCCACCGTTTGCTGTTGACCTGACCATGGAAC  
TTACCAGCACCTGGAATCTAAGGAGTGGTTTGTGCAGCTCTATTACCACGGGAAGGAGCA  
GGTGCCGAGAGGTGCCCCTGATGGGCTCTGCCCGCTGGACATGTTCTTGAATGCCATGTC  
AGTTTATACCTTAAGCCCAGAAAAATACCATGCACTCTGCTCTCAAACCTCAGGTGATGGA  
AGTTGGAATGAAGAGTAACTGATTTATAAAAGCAGGATGTGTTGATTTTAAAATAAAGT  
GCCTTTATACAATG

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**FIGURE 36**

MITGVFSMRLWTPVGVLTSLAYCLHQRRVALAELQEADGQCPVDRSLLKLKMVQVVFRHG  
ARSPLKPLPLEEQVEWNPQLLEVPPQTQFDYTVTNLAGGPKPYSPYDSQYHETTLKGGMF  
AGQLTKVGMQQMFALGERLRKNYVEDIPFLSPTFNPQEVFIRSTNIFRNLESTRCLLAGL  
FQCQKEGPIIIHTDEADSEVLYPNYQSCWSLRQTRGRRTASLQPGISEDLKKVKDRMG  
IDSSDKVDFILLDNVAAEQAHNLPSCPMLKRFAFMIEQRAVDTSLYILPKEDRESLQMA  
VGPFLHILESNNLLKAMDSATAPDKIRKLYLYAAHDVTFIPLLMTLGIFDHKWPPFAVDLT  
MELYQHLESKEWFVQLYYHGKEQVPRGCPDGLCPLDMFLNAMS VYTLSPEKYHALCSQTQ  
VMEVGNEE

**Signal sequence:**

amino acids 1-23

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 218-222

**Casein kinase II phosphorylation site:**

amino acids 87-91, 104-108, 320-324

**Tyrosine kinase phosphorylation site:**

amino acids 280-288

**N-myristoylation site:**

amino acids 15-21, 117-123, 118-124, 179-185, 240-246, 387-393

**Amidation site:**

amino acids 216-220

**Leucine zipper pattern:**

amino acids 10-32

**Histidine acid phosphatases phosphohistidine signature:**

amino acids 50-65

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**FIGURE 37**

ACTGCACTCGGTTCTATCGATTGAATTCCCCGGGGATCCTCTAGAGATCCCTCGACCTCG  
ACCCACGCGTCCGCGGACGCGTGGGCGGACGCGTGGGCGGCTACCAGGAAGAGTCTGCC  
GAAGGTGAAGGCCATGGACTTCATCACCTCCACAGCCATCCTGCCCCCTGCTGTTTCGGCTG  
CCTGGGCGTCTTCGGCCTCTTCCGGCTGCTGCAGTGGGTGCGCGGGAAGGCCTACCTGCG  
GAATGCTGTGGTGGTGATCACAGGCGCCACCTCAGGGCTGGGCAAAGAATGTGCAAAAGT  
CTTCTATGCTGCGGGTGCTAAACTGGTGCTCTGTGGCCGGAATGGTGGGGCCCTAGAAGA  
GCTCATCAGAGAACTTACCGCTTCTCATGCCACCAAGGTGCAGACACACAAGCCTTACTT  
GGTGACCTTCGACCTCACAGACTCTGGGGCCATAGTTGCAGCAGCAGCTGAGATCCTGCA  
GTGCTTTGGCTATGTGACATACTTGTCAACAATGCTGGGATCAGCTACCGTGGTACCAT  
CATGGACACCACAGTGGATGTGGACAAGAGGGTCTGGAGACAAACTACTTTGGCCCAGT  
TGCTCTAACGAAAGCACTCCTGCCCTCCATGATCAAGAGGAGGCAAGGCCACATTGTCGC  
CATCAGCAGCATCCAGGGCAAGATGAGCATTCCTTTTCGATCAGCATATGCAGCCTCCAA  
GCACGCAACCCAGGCTTTCTTTGACTGTCTGCGTGCCGAGATGGAACAGTATGAAATTGA  
GGTGACCGTCATCAGCCCCGGCTACATCCACACCAACCTCTCTGTAAATGCCATCACCGC  
GGATGGATCTAGGTATGGAGTTATGGACACCACCACAGCCCAGGGCCGAAGCCCTGTGGA  
GGTGGCCCAGGATGTTCTTGCTGCTGTGGGGAAGAAGAAGAAAGATGTGATCCTGGCTGA  
CTTACTGCCTTCCTTGGCTGTTTATCTTCGAACTCTGGCTCCTGGGCTCTTCTTCAGCCT  
CATGGCCTCCAGGGCCAGAAAAGAGCGGAAATCCAAGAACTCCTAGTACTCTGACCAGCC  
AGGGCCAGGGCAGAGAAGCAGCACTCTTAGGCTTGCTTACTCTACAAGGGACAGTTGCAT  
TTGTTGAGACTTTAATGGAGATTTGTCTCACAAGTGGGAAAGACTGAAGAAACACATCTC  
GTGCAGATCTGCTGGCAGAGGACAATCAAAAACGACAACAAGCTTCTTCCCAGGGTGAGG  
GGAAACACTTAAGGAATAAATATGGAGCTGGGGTTTAACACTAAAACTAGAAATAAACA  
TCTCAAACAGTAAAAAAAAAAAAAAAAAGGGCGGCCGCGACTCTAGAGTCGACCTGCAGAAG  
CTTGGCCGCCATGGCCCAACTTGTTTATTGTCAGCTTATAATGGTTAC

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**FIGURE 38**

MDFITSTAILPLLFGCLGVFGLFRLLQWVRGKAYLRNAVVVITGATSGLGKECAKVFYAA  
GAKLVLCGRNGGALEELIRELTASHATKVQTHKPYLVTFDLTDSGAIVAAAAEILQCFGY  
VDILVNNAGISYRGTIMDTTVDDVKRVMETNYFGPVALTKALLPSMIKRRQGHIVAIS  
QGKMSIPFRSAYAASKHATQAFFDCLRAEMEQYEIEVTVISPGYIHTNLSVNAITADGSR  
YGVMDTTTAQGRSPVEVAQDVLAAVGKKKKDVILADLLPSLAVYLRTLAPGLFFSLMASR  
ARKERKSKNS

**Signal sequence:**

amino acids 1-21

**Transmembrane domain:**

amino acids 104-120, 278-292

**N-glycosylation site:**

amino acids 228-232

**Glycosaminoglycan attachment site:**

amino acids 47-51

**Casein kinase II phosphorylation site:**

amino acids 135-139, 139-143, 253-257

**Tyrosine kinase phosphorylation site:**

amino acids 145-153, 146-153

**N-myristoylation site:**

amino acids 44-50, 105-111, 238-244, 242-248, 291-297

**Amidation site:**

amino acids 265-269

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 6-17



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**FIGURE 39**

GCAAGCCAAGGCGCTGTTTGAGAAGGTGAAGAAGTTCGGACCCATGTGGAGGAGGGGGACATTGT  
GTACCGCCTCTACATGCGGCAGACCATCATCAAGGTGATCAAGTTCATCCTCATCATCTGTACAC  
CGTCTACTACGTGCACAACATCAAGTTCGACGTGGACTGCACCGTGGACATTGAGAGCCTGACGGG  
CTACCGCACCTACCGCTGTGCCACCCCTGGCCACACTCTTCAAGATCCTGGCGTCTTCTACAT  
CAGCCTAGTCATCTTCTACGGCCTCATCTGCATGTACACACTGTGGTGGATGCTACGGCGCTCCCT  
CAAGAAGTACTCGTTTGAGTCGATCCGTGAGGAGAGCAGCTACAGCGACATCCCCGACGTCAAGAA  
CGACTTCGCCTTCATGCTGCACCTCATTGACCAATACGACCCGCTCTACTCCAAGCGCTTCGCCGT  
CTTCTGTGCGAGGTGAGTGAGAACAAAGCTGCGGCAGCTGAACCTCAACAACGAGTGGACGCTGGA  
CAAGCTCCGGCAGCGGCTCACCAAGAACGCGCAGGACAAGCTGGAGCTGCACCTGTTTCATGCTCAG  
TGGCATCCCTGACACTGTGTTTGACCTGGTGGAGCTGGAGGTCTCAAGCTGGAGCTGATCCCCGA  
CGTGACCATCCCGCCAGCATTGCCAGCTCACGGGCTCAAGGAGCTGTGGCTTACCACACAGC  
GGCCAAGATTGAAGCGCCTGCGCTGGCCTTCTGCGCGAGAACCTGCGGGCGCTGCACATCAAGTT  
CACCGACATCAAGGAGATCCCGCTGTGGATCTATAGCCTGAAGACACTGGAGGAGCTGCACCTGAC  
GGGCAACCTGAGCGCGGAGAACCAACCGCTACATCGTCATCGACGGGCTGCGGGAGCTCAAACGCCCT  
CAAGGTGCTGCGGCTCAAGAGCAACCTAAGCAAGCTGCCACAGGTGGTCAAGATGTGGGCGTGCA  
CCTGCAGAAGCTGTCCATCAACAATGAGGGCACCAAGCTCATCGTCTCAACAGCCTCAAGAAGAT  
GGCGAACCTGACTGAGCTGGAGCTGATCCGCTGCGACCTGGAGCGCATCCCCCACTCCATCTTCAG  
CTTCCACAACCTGCAGGAGATTGACCTCAAGGACAACAACCTCAAGACCATCGAGGAGATCATCAG  
CTTCCAGCACCTGCACCGCCTCACCTGCCCTTAAGCTGTGGTACAACCACATCGCCTACATCCCAT  
CCAGATCGGCAACCTCACCAACCTGGAGCGCCTCTACCTGAACCGCAACAAGATCGAGAAGATCCC  
CACCCAGCTCTTCTACTGCCGCAAGCTGCGCTACCTGGACCTCAGCCACAACAACCTGACCTTCTCT  
CCCTGCCGACATCGGCCCTCTGCAGAACCTCCAGAACCTAGCCATCACGGCCAACCGGATCGAGAC  
GTCTCCCTCCGGAGCTCTTCCAGTGCCGGAAGCTGCGGGCCCTGCACCTGGGCAACAACGTGCA  
GTCACTGCCCTCCAGGGTGGGCGAGCTGACCAACCTGACGCGAGATCGAGCTGCGGGGCAACCGGCT  
GGAGTGCTGCTGTGGAGCTGGGCGAGTGCCCACTGCTCAAGCGCAGCGGCTTGGTGGTGGAGGA  
GGACCTGTTCAACACACTGCCACCCGAGGTGAAGGAGCGGCTGTGGAGGGCTGACAAGGAGCAGGC  
CTGAGCGAGGCCGGCCAGCACAGCAAGCAGCAGGACCGCTGCCAGTCTCAGGCCCGGAGGGGC  
AGGCCTAGCTTCTCCAGAACTCCCGGACAGCCAGGACAGCCTCGCGGCTGGGCGAGGAGCTGGGG  
CCGCTTGTGAGTCAGGCCAGAGCGAGAGGACAGTATCTGTGGGGCTGGCCCTTTTCTCCCTCTGA  
GACTCACGTCCCCAGGGCAAGTGCTTGTGGAGGAGAGCAAGTCTCAAGAGCGCAGTATTTGGATA  
ATCAGGGTCTCCTCCCTGGAGGCCAGCTCTGCCCCAGGGGCTGAGCTGCCACCAGAGGTCCTGGGA  
CCCTCACTTTAGTTCTTGGTATTTATTTTCTCCATCTCCACCTCCTTCATCCAGATAACTTATA  
CATTTCCCAAGAAAGTTTCAGCCAGATGGAAGGTGTTTCAGGGAAGGTGGGCTGCCTTTTCCCTTG  
TCCTTATTTAGCGATGCCGCCGGGCATTTAACACCCACCTGGACTTCAGCAGAGTGGTCCGGGGCG  
AACCAGCCATGGGACGGTCACCCAGCAGTGCCGGGCTGGGCTCTGCGGTGCGGTCCACGGGAGAGC  
AGGCCTCCAGCTGGAAAGGCCAGGCCTGGAGCTTGCCCTTTTCAGTTTTTGTGGCAGTTTTAGTTTT  
TTGTTTTTTTTTTTTTTAATCAAAAAACAATTTTTTTTTAAAAAAGCTTTGAAATGGATGGTTT  
GGGTATTAAGAAAGAAAAAAGCTTAAAAAAGACACTAACGGCCAGTGAGTTGGAGTCTC  
AGGGCAGGGTGGCAGTTTCCCTTGAGCAAAGCAGCCAGACGTTGAACGTGTGTTTCTTCCCTGGG  
CGCAGGGTGCAGGGTGTCTTCCGATCTGGTGTGACCTTGGTCCAGGAGTTCTATTGTTCTTGGG  
GAGGAGGTTTTTTTGTGTTGTTTTTGGGTTTTTTGGTGTCTTGTCTTCTCTCTCCATGTGT  
CTTGGCAGGCATCATTTCTGTGGCTGTGCGCCAGAGGAATGTTCTGGAGCTGCCAAGGGAGGGAG  
GAGACTCGGGTTGGCTAATCCCGGATGAACCGTGCTCCATTGCGACCTCCCTCCTCGTGCCTGC  
CCTGCCTCTCCACGCACAGTGTTAAGGAGCCAAGAGGAGCCACTTCGCCCAGACTTTGTTTCCCA  
CCTCCTGCGGCATGGGTGTGTCCAGTGCCACCGCTGGCCTCCGCTGCTTCCATCAGCCCTGTGCC  
ACCTGGTCTTTCATGAAGAGCAGACACTTAGAGGCTGGTGGGAATGGGGAGGTGCGCCCTGGGAG  
GGCAGGCGTTGGTTCCAAGCCGTTCCCGTCCCTGGCGCCTGGAGTGACACAGCCAGTCGGCAC  
CTGGTGGCTGGAAGCCAACCTGCTTTAGATCACTCGGGTCCCCACCTTAGAAGGGTCCCCGCCTTA  
GATCAATCACGTGGACACTAAGGCAGTTTTAGAGTCTCTGTCTTAATGATTATGTCCATCCGTC  
TGTCCGTCCATTTGTGTTTTCTGCGTCGTGTCATTGGATATAATCCTCAGAAATAATGCACACTAG  
CCTCTGACAACCATGAAGCAAAAATCCGTTACATGTGGGTCTGAACTTGTTAGACTCGGTACAGTA  
TCAAATAAAATCTATAACAGAAAAA

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**FIGURE 40**

MRQTIKVIKFILIIICYTVYYVHNIKFDVDCTVDIESLTGYRTYRCAHPLATLKFILASF  
YISLVIFYGLICMYTLWWMLRRSLKKYSFESIREESSYSDIPDVKNDFAFMLHLIDQYDP  
LYSKRFAVFLSEVSENKLRQLNLNNEWTLDKLRQLTKNAQDKLELHLFMLSIGIPDTVFD  
LVELEVLKLELIPDVTIPPSIAQLTGLKELWLYHTAAKIEAPALAFLRENLRALHIKFTD  
IKEIPLWIYSLKTLEELHLTGNLSAENNRIVIDGLRELKRLKVLRLKSNLSKLPQVVTD  
VGVHLQKLSINNEGTKLIVLNSLKKMANLTELELIRCDLERIPHSIFSLHNLQEIDLKDN  
NLKTIEEIIISFOHLHRLTCLKLWYNHIAIPIQIGNLTNLERLYLNRNKIEKIPTQLFYC  
RKLRYLDLSHNNLTFLPADIGLLQNLQNLAITANRIETLPPELFCRKLRLALHLGNNVLQ  
SLPSRVGELTNLTQIELRGNRLECLPVELGECPLLKRSGLVVEEDLFNTLPPEVKERLWR  
ADKEQA

**Transmembrane domain:**

amino acids 51-75 (type II)

**N-glycosylation site:**amino acids 262-266, 290-294, 328-332, 396-400, 432-436,  
491-495**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 85-89

**Casein kinase II phosphorylation site:**amino acids 91-95, 97-101, 177-181, 253-257, 330-334, 364-368,  
398-402, 493-497**N-myristoylation site:**

amino acids 173-179, 261-267, 395-401, 441-447

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**FIGURE 41**

GGGGGAGAAGGCGGCCGAGCCCCAGCTCTCCGAGCACCGGGTCGGAAGCCGCGACCCGAG  
CCGCGCAGGAAGCTGGGACCGGAACCTCGGCGGACCCGGCCCCACCAACTCACCTGCGC  
AGGTCACCAGCACCCCTCGGAACCCAGAGGCCCGCGCTCTGAAGGTGACCCCCCTGGGGAG  
GAAGGCGATGGCCCCCTGCGAGGACGATGGCCCCGCGCCCGCCTCGCCCCGGCCGGCATCCC  
TGCCGTGCGCTTGTGGCTTCTGTGCACGCTCGGCCTCCAGGGCACCCAGGCCGGGCCACC  
GCCCCGCGCCCCCTGGGCTGCCCCGCGGGAGCCGACTGCCTGAACAGCTTTACCGCCGGGGT  
GCCTGGCTTTCGTGCTGGACACCAACGCCTCGGTGAGCAACGGAGCTACCTTCCTGGAGTC  
CCCCACCGTGCGCCGGGGCTGGGACTGCGTGCGCGCCTGCTGCACCACCCAGAACTGCAA  
CTTGGCGCTAGTGGAGCTGCAGCCCCGACCGCGGGGAGGACGCCATCGCCGCGCTGCTTCCT  
CATCAACTGCCTCTACGAGCAGAACTTCGTGTGCAAGTTTCGCGCCCAGGGAGGGCTTCAT  
CAACTACCTCACGAGGGAAGTGTACCGCTCCTACCGCCAGCTGCGGACCCAGGGCTTTGG  
AGGGTCTGGGATCCCCAAGGCCTGGGCAGGCATAGACTTGAAGGTACAACCCAGGAACC  
CCTGGTGCTGAAGGATGTGGAAAACACAGATTGGCGCCTACTGCGGGGTGACACGGATGT  
CAGGGTAGAGAGGAAAGACCCAAACCAGGTGGAAGTGTGGGGACTCAAGGAAGGCACCTA  
CCTGTTCCAGCTGACAGTGACTAGCTCAGACCACCCAGAGGACACGGCCAACGTACAGT  
CACTGTGCTGTCCACCAAGCAGACAGAAGACTACTGCCTCGCATCCAACAAGGTGGGTGCG  
CTGCCGGGGCTCTTTCCACGCTGGTACTATGACCCACCGAGCAGATCTGCAAGAGTTT  
CGTTTATGGAGGCTGCTTGGGCAACAAGAACAACCTACCTTCGGGAAGAAGAGTGCATTCT  
AGCCTGTGCGGGTGTGCAAGGTGGGCCTTTGAGAGGCAGCTCTGGGGCTCAGGCGACTTT  
CCCCCAGGGCCCCCTCCATGGAAAGGCGCCATCCAGTGTGCTCTGGCACCTGTCAGCCAC  
CCAGTTCCGCTGCAGCAATGGCTGCTGCATCGACAGTTTCCTGGAGTGTGACGACACCCC  
CAACTGCCCCGACGCCTCCGACGAGGCTGCCTGTGAAAAATACACGAGTGGCTTTGACGA  
GCTCCAGCGCATCCATTTCCCAGTGACAAAGGGCACTGCGTGACCTGCCAGACACAGG  
ACTCTGCAAGGAGAGCATCCCGCGCTGGTACTACAACCCCTTCAGCGAACACTGCGCCCCG  
CTTTACCTATGGTGGTTGTTATGGCAACAAGAACAACCTTTGAGGAAGAGCAGCAGTGCCT  
CGAGTCTTGTGCGGGCATCTCCAAGAAGGATGTGTTTGGCCTGAGGCGGGAAATCCCCAT  
TCCCAGCACAGGCTCTGTGGAGATGGCTGTACAGTGTTCCTGGTCATCTGCATTGTGGT  
GGTGGTAGCCATCTTGGGTTACTGCTTCTTCAAGAACCAGAGAAAGGACTTCACCGGACA  
CCACCACCACCCACCCACCCCTGCCAGCTCCACTGTCTCCACTACCGAGGACACGGA  
GCACCTGGTCTATAACCACACCACCCGGCCCCCTCTGAGCCTGGGTCTCACCGGCTCTCAC  
CTGGCCCTGCTTCCTGCTTGCCAAGGCAGAGGCCTGGGCTGGGAAAAACTTTGGAACAG  
ACTCTTGCTGTTTCCCAGGCCCACTGTGCCTCAGAGACCAGGGCTCCAGCCCCCTTTGG  
AGAAGTCTCAGCTAAGCTCACGTCTGAGAAAGCTCAAAGGTTTGGAAGGAGCAGAAAAC  
CCTTGGGCCAGAAGTACCAGACTAGATGGACCTGCCTGCATAGGAGTTTGAGGAAGTTG  
GAGTTTTGTTTCTCTGTTCAAAGCTGCCTGTCCCTACCCCATGGTGCTAGGAAGAGGAG  
TGGGGTGGTGTGAGACCCTGGAGGCCCAACCCTGTCTCCTCCCGAGCTCCTCTTCCATGCT  
GTGCGCCAGGGCTGGGAGGAAGGACTTCCCTGTGTAGTTTGTGCTGTAAAGAGTTGCTT  
TTTGTTTATTTAATGCTGTGGCATGGGTGAAGAGGAGGGGAAGAGGCCTGTTTGGCCTCT  
CTGTCTCTCTTCTTCCCCAAGATTGAGCTCTCTGCCCTTGATCAGCCCCACCCCTG  
GCCTAGACCAGCAGACAGAGCCAGGAGAGGCTCAGCTGCATTCCGCAGCCCCCACCCTG  
AGGTTCTCCAACATCACAGCCAGCCACCCACTGGGTAATAAAAAGTGGTGTGGAAAA  
AAAAAAAAAAAAAAAAAAAAA

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**FIGURE 42**

MAPARTMARARLAPAGIPAVALWLLCTLGLQGTQAGPPPAPPGLPAGADCLNSFTAGVPG  
FVLDTNASVSNGATFLESPTVRRGWDCVRACCTTQNCNLALVELQPDRGEDAIAACFLIN  
CLYEQNFVCKFAPREGFINYLTRVYRSYRQLRTQGFGSGIPKAWAGIDLKVQPQEPLV  
LKDVENTDWRLLRGDTDVRRVERKDPNQVELWGLKEGTYLFQLTVTSSDHPEDTANVTVTV  
LSTKQTEDYCLASNKVGRCRGSFPRWYYDPTEQICKSFVYGGCLGNKNNYLREEECILAC  
RGVQGGPLRGSSGAQATFPQGSPMERHPVCSGTCQPTQFRCSNGCCIDSFLECDTPNC  
PDASDEAAKEYTSGFDELQRIHFPSDKGHCVDLPDTGLCKESIPRWYYPFSEHCARFT  
YGGCYGNKNNFEEEEQQCLESCRGISKKDVFGLRREIPIPISTGSVEMAVTVFLVICIVVVV  
AILGYCFFKNQRKDFHGHHPPTPASSTVSTTEDTEHLVYNHTTRPL

**signal sequence:**

Amino acids 1-35

**transmembrane domain:**

Amino acids 466-483

**N-glycosylation sites:**

Amino acids 66-70;235-239;523-527

**N-myristoylation sites:**

A        m        i        n        o                    a        c        i        d        s  
29-35;43-49;161-167;212-218;281-287;282-288;285-291;  
310-316;313-319;422-428;423-429;426-432

**Cell attachment sequence:**

Amino acids 193-199

**Pancreatic trypsin inhibitor (Kunitz) family signatures:**

Amino acids 278-298;419-438

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**FIGURE 43**

CCCACGCGTCCGCACCTCGGCCCCGGGCTCCGAAGCGGCTCGGGGGCGCCCTTTTCGGTCA  
ACATCGTAGTCCACCCCCTCCCCATCCCCAGCCCCCGGGGATTTCAGGCTCGCCAGCGCCC  
AGCCAGGGAGCCGGCCGGGAAGCGCGATGGGGGCCCCAGCCGCTCGCTCCTGCTCCTGC  
TCCTGCTGTTTCGCCTGCTGCTGGGCGCCCCGGCGGGGCCAACCTCTCCAGGACGACAGCC  
AGCCCTGGACATCTGATGAAACAGTGGTGGCTGGTGGCACCGTGGTGGTCAAGTGCCAAG  
TGAAAGATCACGAGGACTCATCCCTGCAATGGTCTAACCTGCTCAGCAGACTCTCTACT  
TTGGGGAGAAGAGAGCCCTTCGAGATAATCGAATTCAGCTGGTTACCTCTACGCCCCACG  
AGCTCAGCATCAGCATCAGCAATGTGGCCCTGGCAGACGAGGGCGAGTACACCTGCTCAA  
TCTTCACTATGCCTGTGCGAACTGCCAAGTCCCTCGTCACTGTGCTAGGAATTCCACAGA  
AGCCCATCATCACTGGTTATAAATCTTCATTACGGGAAAAAGACACAGCCACCCTAAACT  
GTCAGTCTTCTGGGAGCAAGCCTGCAGCCCGGCTCACCTGGAGAAAGGGTGACCAAGAAC  
TCCACGGAGAACCAACCCGCATACAGGAAGATCCCAATGGTAAAACCTTCACTGTCAGCA  
GCTCGGTGACATTCAGGTTACCCGGGAGGATGATGGGGCGAGCATCGTGTGCTCTGTGA  
ACCATGAATCTCTAAAGGGAGCTGACAGATCCACCTCTCAACGCATTGAAGTTTTATACA  
CACCAACTGCGATGATTAGGCCAGACCCTCCCCATCCTCGTGAGGGCCAGAAGCTGTTGC  
TACACTGTGAGGGTCGCGGCAATCCAGTCCCCCAGCAGTACCTATGGGAGAAGGAGGGCA  
GTGTGCCACCCCTGAAGATGACCCAGGAGAGTGCCCTGATCTTCCCTTTCTCAACAAGA  
GTGACAGTGGCACCTACGGCTGCACAGCCACCAGCAACATGGGCAGCTACAAGGCCTACT  
ACACCCTCAATGTTAATGACCCCAGTCCGGTGCCCTCCTCCTCCAGCACCTACCACGCCA  
TCATCGGTGGGATCGTGGCTTTCATTGTCTTCTGCTGCTCATCATGCTCATCTTCCTTG  
GCCACTACTTGATCCGGCACAAAGGAACCTACCTGACACATGAGGCAAAAGGCTCCGACG  
ATGCTCCAGACGCGGACACGGCCATCATCAATGCAGAAGGCGGGCAGTCAGGAGGGGACG  
ACAAGAAGGAATATTTTCATCTAGAGGCGCCTGCCCACTTCCTGCGCCCCCAGGGGCCCC  
GTGGGGACTGCTGGGGCCGTCACCAACCCGGACTTGTACAGAGCAACCGCAGGGCCGCCC  
CTCCCGCTTGCTCCCCAGCCACCCACCCCTGTACAGAATGTCTGCTTTGGGTGCGGT  
TTTGTACTCGGTTTGAATGGGGAGGGAGGAGGGCGGGGGAGGGGAGGGTTGCCCTCAG  
CCCTTTCGCTGGCTTCTCTGCATTGTTGGGTATTATTATTTTGTAAACAATCCCAATCAA  
ATCTGTCTCCAGGCTGGAGAGGCAGGAGCCCTGGGGTGAGAAAAGCAAAAACAAACAAA  
AAACA

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**FIGURE 44**

MGAPAASLLLLLLLLFACCWAPGGANLSQDDSQPWTSDETVVAGGTVVLKCQVKDHEDSSL  
QWSNPAQQTLYFGEKRALRDNRIQLVTSTPHELSSISNVALADEGEYTCSTFTMPVRTA  
KSLVTVLGIPQKPIITGYKSSLREKDTATLNCQSSGSKPAARLTWRKGDQELHGEPTRIQ  
EDPNGKTFTVSSSVTFQVTRREDDGASIVCSVNHESLKGADRSTSQRIEVLYTPTAMIRPD  
PPHPREGQKLLHCEGRGNPVPQQYLWEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCT  
ATSNMGSYKAYYTLNVNDPSPVPSSSSTYHAIIGGIVAFIVFLLLIIMLIFLGHYLIIRHKG  
TYLTHEAKGSDDAPDADTAIINAEGGQSGGDDKKEYFI

**Signal sequence:**

amino acids 1-20

**Transmembrane domain:**

amino acids 331-352

**N-glycosylation site:**

amino acids 25-29, 290-294

**Casein kinase II phosphorylation site:**

amino acids 27-31, 35-39, 89-93, 141-145, 199-203, 388-392

**N-myristoylation site:**amino acids 2-8, 23-29, 156-162, 218-224, 295-301, 298-304,  
306-310, 334-340, 360-364, 385-389, 386-390**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 7-18

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**FIGURE 45**

ACTTGCCATCACCTGTTGCCAGTGTGGAAAAATTCTCCCTGTTGAATTTTTTGCACATGG  
AGGACAGCAGCAAAGAGGGCAACACAGGCTGATAAGACCAGAGACAGCAGGGAGATTATT  
TTACCATACGCCCTCAGGACGTTCCCTCTAGCTGGAGTTCTGGACTTCAACAGAACCCCA  
TCCAGTCATTTTGATTTTGCTGTTTATTTTTTTTTTTCTTTTTCTTTTTCCCACCACATTG  
TATTTTATTTCCGTACTTCAGAAATGGGCCTACAGACCACAAAGTGGCCCAGCCATGGGG  
CTTTTTTCTGAAGTCTTGGCTTATCATTTCCCTGGGGCTCTACTCACAGGTGTCCAAAC  
TCCTGGCCTGCCCTAGTGTGTGCCGCTGCGACAGGAACCTTGTCTACTGTAATGAGCGAA  
GCTTGACCTCAGTGCCTCTTGGGATCCCGGAGGGCGTAACCGTACTCTACCTCCACAACA  
ACCAAATTAATAATGCTGGATTTCCTGCAGAACTGCACAATGTACAGTCGGTGCACACGG  
TCTACCTGTATGGCAACCAACTGGACGAATTCCTCATGAACCTTCCCAAGAATGTCAGAG  
TTCTCCATTTGCAGGAAAACAATATTAGACCATTTACGGGCTGCTCTTGCCCAGCTCT  
TGAAGCTTGAAGAGCTGCACCTGGATGACAACCTCCATATCCACAGTGGGGGTGGAAGACG  
GGGCTTCCGGGAGGCTATTAGCCTCAAATTGTTGTTTTGTCTAAGAATCACCTGAGCA  
GTGTGCCTGTTGGGCTTCTGTGGACTTGCAAGAGCTGAGAGTGGATGAAAATCGAATTG  
CTGTCATATCCGACATGGCCTTCCAGAATCTCACGAGCTTGGAGCGTCTTATTGTGGACG  
GGAACCTCCTGACCAACAAGGGTATCGCCGAGGGCACCTTCAGCCATCTCACCAAGCTCA  
AGGAATTTTCAATTGTACGTAATTGCTGTCCACCCTCCTCCCGATCTCCCAGGTACGC  
ATCTGATCAGGCTCTATTTGCAGGACAACCAGATAAACACATTCCTTTGACAGCCTTCT  
CAAATCTGCGTAAGCTGGAACGGCTGGATATATCCAACAACCAACTGCGGATGCTGACTC  
AAGGGGTTTTTGATAATCTCTCCAACCTGAAGCAGCTCACTGCTCGGAATAACCCCTGGT  
TTTGTGACTGCAGTATTAAATGGGTACAGAATGGCTCAAATATATCCCTTCATCTCTCA  
ACGTGCGGGGTTTCATGTGCCAAGGTCTGAACAAGTCCGGGGGATGGCCGTGAGGGAAT  
TAAATATGAATCTTTTGTCTGTCCACCACGACCCCCGGCCTGCCTCTCTTACCCCCAG  
CCCCAAGTACAGCTTCTCCGACCACTCAGCCTCCCACCCTCTCTATTCCAAACCCCTAGCA  
GAAGCTACACGCCTCCAACCTCCTACCACATCGAACTTCCCACGATTCTCTGACTGGGATG  
GCAGAGAAAGAGTGACCCACCTATTTCTGAACGGATCCAGCTCTCTATCCATTTTGTGA  
ATGATACTTCCATTCAAGTCAGCTGGCTCTCTCTCTTACCCTGATGGCATACAAACCTCA  
CATGGGTGAAAATGGGCCACAGTTTAGTAGGGGGCATCGTTTCAGGAGCGCATAGTCAGCG  
GTGAGAAGCAACACCTGAGCCTGGTTAACTTAGAGCCCCGATCCACCTATCGGATTTGTT  
TAGTGCCACTGGATGCTTTTAACTACCGCGCGGTAGAAGACACCATTTGTTTCAGAGGCCA  
CCACCCATGCCTCCTATCTGAACAACGGCAGCAACACAGCGTCCAGCCATGAGCAGACGA  
CGTCCACAGCATGGGCTCCCCCTTTCTGCTGGCGGGCTTGATCGGGGGCGCGGTGATAT  
TTGTGCTGGTGGTCTTGCTCAGCGTCTTTTGTGTCATATGCACAAAAGGGGCGCTACA  
CCTCCAGAAAGTGGAATACAACCGGGGCGGGCGGAAAGATGATTATTGCGAGGCAGGCA  
CCAAGAAGGACAACTCCATCCTGGAGATGACAGAAACAGTTTTTCAGATCGTCTCTTAA  
ATAACGATCAACTCCTTAAAGGAGATTTAGACTGCAGCCCATTTACACCCCAAATGGGG  
GCATTAATTACACAGACTGCCATATCCCCAACACATGCGATACTGCAACAGCAGCGTGC  
CAGACCTGGAGCACTGCCATACGTGACAGCCAGAGGCCAGCGTTATCAAGGCGGACAAT  
TAGACTCTTGAGAACACACTCGTGTGTGCACATAAAGACACGCAGATTACATTTGATAAA  
TGTTACACAGATGCATTTGTGCATTTGAATACTCTGTAATTTATACGGTGTACTATATAA  
TGGGATTTAAAAAAGTGCTATCTTTTCTATTTCAAGTTAATTACAAACAGTTTTGTAA  
TCTTTGCTTTTAAATCTT

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**FIGURE 46**

MGLQTTKWPSHGAFFLKSWLIISLGLYSQVSKLLACPSVCRCDRNFVYCNERSLTSVPLG  
IPEGVTVLVYLHNNQINNAGFPAELHNVQSVHTVYLYGNQLDEFPMNLPKNVRVLHLQENN  
IQTISRALAQLLKLEELHLDDNSISTVGVEDGAFREAIKLLFLSKNHLSSVPVGLPV  
DLQELRVDENRIAVISDMAFQNLTSLERLIVDGNLLTNKGIAEGTFSHLTKLKEFSIVRN  
SLSHPPPDLPGTHLIRLYLQDNQINHIPLTAFSNLRKLERLDISNNQLRMLTQGVFDNLS  
NLKQLTARNNPWFCDCSIKWVTEWLKYIPSSLNVRGFMCGPEQVRGMVAVRELNMNLLSC  
PTTTPGLPLFTPAPSTASPTTQPPTLSIPNPSRSYTPPTPTTSKLPTIPDWDGRERVTPP  
ISERIQLSIHFVNDTSIQVSWLSLFTVMAYKLTWVKMGHSLVGGIVQERIVSGEKQHLSL  
VNLEPRSTYRICLVPLDAFNRYRAVEDTICSEATTHASYLNNGSNTASSHEQTTSMSGSP  
FLLAGLIGGAVIFVLVVLLSVFCWHMHKKGRTYSQKWKNRGRKDDYCEAGTKKDNSIL  
EMTETSFQIVSLNNDQLLKGD FRLQPIYTPNGGINYTDCHI PNNMRYCNSSVPDLEHCHT

**Signal peptide:**  
amino acids 1-42

**Transmembrane domain:**  
amino acids 542-561

**N-glycosylation site:**  
amino acids 202-206, 298-302, 433-437, 521-525, 635-639,  
649-653

**Casein kinase II phosphorylation site:**  
amino acids 204-208, 407-411, 527-531, 593-597, 598-602,  
651-655

**Tyrosine kinase phosphorylation site:**  
amino acids 319-328

**N-myristoylation site:**  
amino acids 2-8, 60-66, 149-155, 213-219, 220-226, 294-300,  
522-528, 545-551, 633-639

**Amidation site:**  
amino acids 581-585

**Leucine zipper pattern:**  
amino acids 164-186

**Phospholipase A2 aspartic acid active site:**  
amino acids 39-50



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**FIGURE 47**

GCAGCGAGCGCCGGGTGCGGCCCTGCCGCCGCAGGGATGTGACCTTCACCGTCGCTTAGC  
CAGGATGACCGGAGCCCGTGTCTCGCGCGTCCGCGCCTCGCTTCAGCCTCCCGGGTGCT  
CTGACCGCACGCTCCCGGCTGCTAGGCTCCCCGGCACCGGCCTCGCCATGCCGCCACCGC  
CCGGGCCCGCCGCCGCCCTGGGCACTGCGCTTCTGCTGCTCCTGCTGGCTTCCGAGTCTT  
CTCACACTGTGCTGTTGCGGGCGCGTGAGGCGGCGCAGTTTCTGCGGCCAGGCAGCGCC  
GCGCCTACCAAGTCTTCGAGGAGGCCAAGCAGGGCCACCTGGAACGGGAGTGCGTGGAGG  
AGGTGTGCAGCAAAGAGGAGGCCAGAGAGGTGTTGAGAACGACCCCGAGACGGAGTATT  
TCTATCCACGATATCAAGAGTGCATGAGAAAATATGGCAGGCCTGAAGAAAAAACCAG  
ATTTCCGCAAATGTGTTCAGAACCTGCCTGACCAGTGCACCCCAAACCCTTGTGATAAGA  
AGGGTACTCATATCTGCCAAGACCTCATGGGCAACTTCTTCTGCGTGTGCACAGATGGCT  
GGGGAGGCCGGCTCTGTGACAAAGATGTCAATGAGTGTGTCCAGAAGAATGGGGGCTGCA  
GCCAGGTCTGCCACAACAAACCAGGAAGCTTCCAATGTGCCTGCCATAGTGGCTTCTCGC  
TTGCATCAGACGGCCAGACCTGCCAAGATATCGATGAATGCACAGACTCAGACACCTGTG  
GGGACGCGCGATGCAAGAACTTGCCAGGCTCCTACTCTTGCCCTCTGCGATGAGGGATATA  
CATACAGCTCCAAGGAGAAGACCTGCCAAGATGTGGACGAGTGCCAGCAGGATCGCTGTG  
AGCAGACCTGTGTCAACTCCCAGGCAGCTATACCTGCCACTGTGATGGGCGAGGGGGCC  
TAAACTATCCCCAGACATGGATACTTGTGAGGACATCTTACCATGTGTGCCCTTCAGCA  
TGGCCAAGAGCGTGAAGTCCTTGTACCTGGGCCGCATGTTTCAGCGGGACCCCCGTGATTA  
GACTACGCTTCAAGAGGCTTCAGCCTACCAGGCTGCTGGCTGAATTTGACTTCCGCACTT  
TTGACCCTGAAGGAGTCCTCTTCTTCGCTGGAGGCCGTTTCAGACAGCACCTGGATTGTCC  
TGGGCCTAAGAGCTGGGCGGCTTGAGCTGCAGCTTCGGTACAATGGCGTTGGGCGCATCA  
CCAGCAGCGGGCCAACCATCAACCACGGCATGTGGCAAACCTATCTCCGTGGAAGAGCTGG  
AACGTAACCTTGTCAATCAAGGTCAACAAAGATGCTGTAATGAAGATCGCGGTAGCTGGGG  
AGCTGTTTCAGCTGGAGAGGGGCTCTATCACCTGAATCTCACCGTGGGCGGCATTCCCT  
TCAAGGAGAGTGAGCTCGTCCAGCCGATTAACCCTCGCCTGGATGGGTGCATGAGGAGTT  
GGAACCTGGCTGAACGGGGAAGACAGCGCCATCCAGGAGACAGTCAAGGCAAACACAAAA  
TGCAGTGCTTCTCTGTGACAGAAAGGGGCTCCTTCTTCCCGGGGAATGGATTGTCTACCT  
ACAGGCTCAACTACACCCGAACATCGCTGGATGTGGCACGGAAACCACCTGGGAAGTTA  
AAGTTGTGGCTCGGATCCGCCCTGCCACGGACACGGGGGTGCTGCTGGCGCTGGTGGGGG  
ACGACGATGTCGTCTCTGTGGCCCTAGTCGACTACCACTCTACAAAGAAGCTCAAGA  
AGCAGTTGGTGGTCTTGGCAGTTGAGGATGTTGCCCTGGCACTGATGGAAATCAAGGTGT  
GCGACAGCCAGGAACACACGGTCACTGTCTCCCTGCGGGAGGGTGAGGCCACCCTAGAAG  
TGGATGGCACAAAGGGCCAGAGTGAAGTGAGCACTGCCAGCTGCAGGAGCGACTGGACA  
CACTTAAGACACATCTGCAAGGCTCTGTGCACACCTATGTTGGAGGCCTGCCAGAAGTAT  
CGGTGATTTCTGCACCCGTCCTGCGTTCTACCGCGGATGCATGACTCTGGAGGTAAACG  
GGAAAATCCTGGACCTGGATACGGCCTCGTACAAGCACAGTGACATCACCTCCCCTCCT  
GCCCCCTGTGGAGCATGCCACCCCCTAGACCGAGCTGCAAGAGGGCTCCACACCTAAAG  
ACAAAAATGAAGCAGGGTTTGGACACACAGCACTGGCTCCTCTCGCATGGTCTCTGCAACA  
CTGGAGCAGCGTGGACCGCCCTTGTGGTTTTTTTTTTCTTGAGATCTTCTTTTTTGCCTTG  
TAACATATCTGTACATAATGGACGGGTGTGGGTACACGGCTGCTCAGAGAGAGCCACGT  
GACCTGGTGGGAGCTGGCTGGAAGGGGCTGGGCTAGAGGGGCTGGCAGTTTGCAGCAGAA  
CGGATGTGAAGAAAATAATTCTCTATTATTTTATTACTACATGCTTCTTTCTGACTCTA  
AAATATGGAATAAAATATTTACAGAAACCTTTTTAAAAA

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**FIGURE 48**

MPPPPGPAAALGTALLLLLLLASESSHTVLLRAREAAQFLRPRQRRAYQVFEEAKQGHLE  
ECVVEVCSKEEAREVFENDPETEYFYPRYQECMRKYGRPEEKNPDFAKCVQNLDPDQCTPN  
PCDKKGTTHICQDLMGNFVCVCTDGGWGGRLCDKDVNECVQKNGGCSQVCHNKPGSFQCA  
SGFSLASDGQTCQDIDECTDSDTCGDARCKNLPGSYSLCDEGYTYSSKEKTCQDVDECQ  
QDRCEQTCVNSPGSYTCHCDGRGGLKLSPDMDTCEDILPCVPFMAKSVKSLYLGRMFSG  
TPVIRLRFKRLQPTRLLAEFDFRTFDPEGVLFFAGGRSDSTWIVLGLRAGRLELQLRYNG  
VGRITSSGPTINHG MWQTISVEELERNLVIKVNKDAVMKIAVAGELFQLERGLYHLNLT  
GGIPFKESELVQPINPRLDGCMRSWNWLNGEDSAIQETVKANTKMQCFSVTERGSFFPGN  
GFATYRLNYTRTSLDVGTETTWEVKVVARIRPATDTGVLLALVGDDDVVISVALVDYHST  
KKLKKQLVVLAVEDVALALMEIKVCDSEHTVTVSLREGEATLEVDGTKGQSEVSTAQLQ  
ERLDTLKTHLQGSVHTYVGGLPEVSVISAPVTA FYRGCMTELVNGKILDLDTASYKHSDI  
TSHSCPPVEHATP

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**FIGURE 49**

CGCCGCGCTCCCGCACCCGCGGCCCGCCACCGCGCCGCTCCCGCATCTGCACCCGCAGC  
CCGGCGGCCTCCCGGCGGGAGCGAGCAGATCCAGTCCGGCCCGCAGCGCAACTCGGTCCA  
GTCGGGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCTGCTGT  
GCCTGCTGCTGGCGGGCGGCGGTCCCCACGGCCCCCGCGCCCGCTCCGACGGCGACCTCGG  
CTCCAGTCAAGCCCGGCCCGGCTCTCAGCTACCCGCAGGAGGAGGCCACCCTCAATGAGA  
TGTTCCGCGAGGTTGAGGAACTGATGGAGGACACGCAGCACAAATTGCGCAGCGCGGTGG  
AAGAGATGGAGGCAGAAGAAGCTGCTGCTAAAGCATCATCAGAAGTGAACCTGGCAAACCT  
TACCTCCAGCTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCC  
ATGTGCACCGAGAAATTCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAG  
AGACAGTTATCACATCTGTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCG  
ACGAGGACTGTGGGCCCAGCATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGC  
CATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACAGTGAGTGCTGTGGAGACCAGCTGT  
GTGTCTGGGGTCACTGCACCAAAATGGCCACCAGGGGCAGCAATGGGACCATCTGTGACA  
ACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCTTCCAGAGAGGCCCTGCTGTTCCCTG  
TGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACCCCGCCAGCCGGCTTCTGG  
ACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGATGCCCTTGTGCCAGTG  
GCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGCCGACCTTCGTGG  
GGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTCCCCGATGAGTATGAAG  
TTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGGAGCCTGACTG  
AAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGAGGGGAAGAGA  
TTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCCCCA  
GGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCTACATCTTCTTCCAGTAAGTT  
TCCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTTCAGCTCCCCCAGGCTGTTCT  
CCAGGCTTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTT  
GCCACCCCTGTCCAGATTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGT  
TCTACATGGCTTTGATAATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTC  
TGATTGGTTTTGGGAAATGTGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAA  
AAATGCAACAAATGAATTTTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTT  
CAGCTGTTGCAGATGAAATGTTCTGTTACCCCTGCATTACATGTGTTTATTTCATCCAGCA  
GTGTTGCTCAGCTCCTACCTCTGTGCCAGGGCAGCATTTTCATATCCAAGATCAATTCCC  
TCTCTCAGCACAGCCTGGGGAGGGGGTCATTGTTCTCCTCGTCCATCAGGGATCTCAGAG  
GCTCAGAGACTGCAAGCTGCTTGCCCAAGTCACACAGCTAGTGAAGACCAGAGCAGTTTC  
ATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTCCACTACCCACACCAGCCTTGGTGCCA  
CCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTGAGGCATGCACATCTGGA  
ATTAAGGTCAAACATAATTCTCACATCCCTCTAAAAGTAACTACTGTTAGGAACAGCAGT  
GTTCTCACAGTGTGGGGCAGCCGTCTTCTAATGAAGACAATGATATTGACACTGTCCCT  
CTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCGTAGCATAACAGGTTAA  
CCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAT  
CACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGGC  
TGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAA  
TGATGTTTTAGGTGTGATGGACTGTTGCCACCATGTATTTCATCCAGAGTTCTTAAAGTT  
TAAAGTTGCACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACAT  
AAGTTGCATTTAGAAATCAAGCATAAATCACTTCAACTGCAAAAAAAAAAAAAAAAAAAAA  
AAAAAA

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**FIGURE 50**

MQRLGATLLCLLLAAVPTAPAPAPTATSAPVKPGPALSYPQEEATLNEMFREVEELMED  
TQHKLRSAVEEMEAEEAAAKASSEVNLANLPSPYHNETNTDTKVGNNNTIHVHREIHKITN  
NQTGQMVFSETVITSVGDEEGRRSHECIIDEDCGPSMYCQFASFQYTCQPCRGQRMCTR  
DSECCGDQLCVWGHCTKMATRGSNGTICDNQRDCQPGLCFAFQRGLLFPVCTPLPVEGEL  
CHDPASRLLDLITWELEPDGALDRCPASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILL  
PREVPDEYEVGSFMEEVRQELEDLERSLTEEMALGEPAAAAAALLGGEEI

**Signal sequence:**

amino acids 1-19

**N-glycosylation site:**

amino acids 96-100, 106-110, 121-125, 204-208

**Casein kinase II phosphorylation site:**amino acids 46-50, 67-71, 98-102, 135-139, 206-210, 312-316,  
327-331**N-myristoylation site:**

amino acids 202-208, 217-223

**Amidation site:**

amino acids 140-144

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**FIGURE 51**

GCCTGTTGCTGATGCTGCCGTGCGGTACTTGTCATGGGAGCTGGCACTGCGGCGCTCTCCC  
GTCCCGCGGTGGTTGCTGCTGCTGCCGTGCTGCTGGGCCTGAACGCAGGAGCTGTCATT  
GACTGGCCCCACAGAGGAGGGCAAGGAAGTATGGGATTATGTGACGGTCCGCAAGGATGCC  
TACATGTTCTGGTGGCTCTATTATGCCACCAACTCCTGCAAGAACTTCTCAGAACTGCCC  
CTGGTCATGTGGCTTCAGGGCGGTCCAGGCGGTTCTAGCACTGGATTGGAACCTTTGAG  
GAAATTGGGCCCCCTTGACAGTGATCTCAAACCACGGAAAACCACCTGGCTCCAGGCTGCC  
AGTCTCCTATTTGTGGATAATCCCGTGGGCACTGGGTTCAAGTTATGTGAATGGTAGTGGT  
GCCTATGCCAAGGACCTGGCTATGGTGGCTTCAGACATGATGGTTCTCCTGAAGACCTTC  
TTCAGTTGCCACAAAGAATTCAGACAGTTCCATTCTACATTTTCTCAGAGTCCTATGGA  
GGAAAAATGGCAGCTGGCATTGGTCTAGAGCTTTATAAGGCCATTACAGCGAGGGACCATC  
AAGTGCAACTTTGCGGGGGTTGCCTTGGGTGATTCTCTGGATCTCCCCTGTTGATTGCGGTG  
CTCTCCTGGGGACCTTACCTGTACAGCATGTCTCTTCTCGAAGACAAAGGTCTGGCAGAG  
GTGTCTAAGGTTGCAGAGCAAGTACTGAATGCCGTAAATAAGGGGCTCTACAGAGAGGCC  
ACAGAGCTGTGGGGGAAAGCAGAAATGATCATTGAACAGAACACAGATGGGGTGAACCTTC  
TATAACATCTTAACTAAAAGCACTCCACGTCTACAATGGAGTCGAGTCTAGAATTCACA  
CAGAGCCACCTAGTTTGTCTTTGTGTCAGCGCCACGTGAGACACCTACAACGAGATGCCTTA  
AGCCAGCTCATGAATGGCCCCATCAGAAAGAAGCTCAAATTTATTCCTGAGGATCAATCC  
TGGGGAGGCCAGGCTACCAACGTCTTTGTGAACATGGAGGAGGACTTCATGAAGCCAGTC  
ATTAGCATTGTGGACGAGTTGCTGGAGGCAGGGATCAACGTGACGGTGTATAATGGACAG  
CTGGATCTCATCGTAGATACCATGGGTGAGGAGGCTGGGTGCGGAACTGAAGTGGCCA  
GAACTGCCTAAATTCAGTCAGCTGAAGTGAAGGCCCTGTACAGTGACCCTAAATCTTTG  
GAAACATCTGCTTTTGTCAAGTCCTACAAGAACCTTGCTTTCTACTGGATTCTGAAAGCT  
GGTCATATGGTTCCTTCTGACCAAGGGGACATGGCTCTGAAGATGATGAGACTGGTGACT  
CAGCAAGAATAGGATGGATGGGGCTGGAGATGAGCTGGTTTGGCCTTGGGGCACAGAGCT  
GAGCTGAGGCCGCTGAAGCTGTAGGAAGCGCCATTCTTCCCTGTATCTAACTGGGGCTGT  
GATCAAGAAGGTTCTGACCAGCTTCTGCAGAGGATAAAATCATTGTCTCTGGAGGCAATT  
TGGAATTTATTTCTGCTTCTTAAAAAACCTAAGATTTTTTAAAAAATTGATTTGTTTTG  
ATCAAAATAAAGGATGATAATAGATATTAA

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**FIGURE 52**

MELALRRSPVPRWLLLLPLLLGLNAGAVIDWPTEEGKEVWDYVTVRKDAYMFWWLYYATN  
SCKNFSELPLVMWLQGGPGGSSTGFGNFEEIGPLDSLKPRKTTWLQAASLLFVDNPVGT  
GFSYVNGSGAYAKDLAMVASDMMVLLKTFFSCHKEFQTVPFYIFSESYGGKMAAGIGLEL  
YKAIQRGTIKCNFAGVALGDSWISPVDSVLSWGPYLYSMSLLEDKGLAEVSKVAEQVLNA  
VNKGLYREATLWGKAEMIEQNTDGVNFYNILTKSTPTSTMESSLEFTQSHLVCLCQRH  
VRHLQDALSQLMNGPIRKCLKIIPEDQSWGGQATNVFVNMEEDFMKPVISIVDELLEAG  
INVTVYNGQLDLIVDTMGQEAWVRKLKWPELPKFSQLKWKALYSDPKSLETSAFVKS YKN  
LAFYWILKAGHMVPSDQGDMA LKMMRLVTQQE

**Signal sequence:**

amino acids 1-25

**N-glycosylation site:**

amino acids 64-68, 126-130, 362-366

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 101-105

**Casein kinase II phosphorylation site:**amino acids 204-208, 220-224, 280-284, 284-288, 351-355,  
449-453**N-myristoylation site:**amino acids 22-28, 76-82, 79-85, 80-86, 119-125, 169-175,  
187-193, 195-201, 331-337, 332-338, 360-366

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**FIGURE 53**

GTCTGTTCCCAGGAGTCCTTCGGCGGCTGTTGTGTCA GTGGCCTGATCGCGATGGGGACA  
AAGGCGCAAGTCGAGAGGAACTGTTGTGCCTCTTCATATTGGCGATCCTGTTGTGCTCC  
CTGGCATTGGGCAGTGTTACAGTGCCTCTTCTGAACCTGAAGTCAGAATTCCTGAGAAT  
AATCCTGTGAAGTTGTCTGTGCCTACTCGGGCTTTTCTTCTCCCCGTGTGGAGTGGAAG  
TTTGACCAAGGAGACACCACCAGACTCGTTTGCTATAATAACAAGATCACAGCTTCCTAT  
GAGGACCGGGTGACCTTCTTGCCAACTGGTATCACCTTCAAGTCCGTGACACGGGAAGAC  
ACTGGGACATACACTTGTATGGTCTCTGAGGAAGGCGGCAACAGCTATGGGGAGGTCAAG  
GTCAAGCTCATCGTGCTTGTGCCTCCATCCAAGCCTACAGTTAACATCCCCCTCCTCTGCC  
ACCATTTGGGAACCGGGCAGTGCTGACATGCTCAGAACAAGATGGTTCCCCACCTTCTGAA  
TACACCTGGTTCAAAGATGGGATAGTGATGCCTACGAATCCCAAAGCACCCGTGCCTTC  
AGCAACTCTTCTATGTCTGAATCCCACAACAGGAGAGCTGGTCTTTGATCCCCCTGTCA  
GCCTCTGATACTGGAGAATACAGCTGTGAGGCACGGAATGGGTATGGGACACCCATGACT  
TCAATGCTGTGCGCATGGAAGCTGTGGAGCGGAATGTGGGGGTCTCGTGGCAGCCGTC  
CTTGTAACCCTGATTCTCCTGGGAATCTTGTTTTTGGCATCTGGTTTGCCTATAGCCGA  
GGCCACTTTGACAGAACAAAGAAAGGGACTTCGAGTAAGAAGGTGATTTACAGCCAGCCT  
AGTGCCCGAAGTGAAGGAGAATTCAAACAGACCTCGTCATTCTGGTGTGAGCCTGGTCG  
GCTCACCGCCTATCATCTGCATTTGCCTTACTCAGGTGCTACCGGACTCTGGCCCCTGAT  
GTCTGTAGTTTACAGGATGCCTTATTTGTCTTCTACACCCACAGGGCCCCCTACTTCT  
TCGGATGTGTTTTTAATAATGTCAGCTATGTGCCCCATCCTCCTTCATGCCCTCCCTCCC  
TTTCTTACCACTGCTGAGTGGCCTGGAACCTGTTTAAAGTGTTTATTCCCCATTTCTTTG  
AGGGATCAGGAAGGAATCCTGGGTATGCCATTGACTTCCCTTCTAAGTAGACAGCAAAAA  
TGGCGGGGGTTCGAGGAATCTGCACTCAACTGCCACCTGGCTGGCAGGGATCTTTGAAT  
AGGTATCTTGAGCTTGGTTCTGGGCTCTTTCCTTGTGTACTGACGACCAGGGCCAGCTGT  
TCTAGAGCGGGAATTAGAGGCTAGAGCGGCTGAAATGGTTGTTTGGTGATGACACTGGGG  
TCCTTCCATCTCTGGGGCCCACTCTCTTCTGTCTTCCCATGGGAAGTGCCACTGGGATCC  
CTCTGCCCTGTCTCCTGAATACAAGCTGACTGACATTGACTGTGTCTGTGGAAAATGGG  
AGCTCTTGTTGTGGAGAGCATAGTAAATTTTCAGAGAACTTGAAGCCAAAAGGATTTAAA  
ACCGCTGCTCTAAAGAAAAGAAAACCTGGAGGCTGGGCGCAGTGGCTCACGCCTGTAATCC  
CAGAGGCTGAGGCAGGCGGATCACCTGAGGTGGGAGTTCTGGGATCAGCCTGACCAACAT  
GGAGAAACCCTACTGGAAATACAAAGTTAGCCAGGCATGGTGGTGCATGCCTGTAGTCCC  
AGCTGCTCAGGAGCCTGGCAACAAGAGCAAACTCCAGCTCAAAAAAAAAAAAAAAAAA

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**FIGURE 54**

MGTKAQVERKLLCLFILAILLCSLALGSVTVHSSEPEVRIPENNPVKLS CAYSGFSSPRV  
EWKFDQGD TTRLVCYNNKITASYEDRV TFLPTGITFKSVTREDTGT YTCMVSEEGNSYG  
EVKVKLIVLVPPSKPTVNI PSSATIGNRAVLTCSEQDGSPPSEYTWFKDGI VMPTNPKST  
RAFSNSSYVLNPTTGELVFDPLSASDTGEYSCEARNGYGTPMTSNAVRMEAVERNVG VIV  
AAVLVTLILLGILVFGIWFAYS RGHFDR TKKGTSSKKVIYSQPSARSEGEFKQTSSFLV

**Signal sequence:**  
amino acids 1-27

**Transmembrane domain:**  
amino acids 238-255

**N-glycosylation site:**  
amino acids 185-189

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 270-274

**Casein kinase II phosphorylation site:**  
amino acids 34-38, 82-86, 100-104, 118-122, 152-156,  
154-158, 193-197, 203-207, 287-291

**N-myristoylation site:**  
amino acids 105-111, 116-122, 158-164, 219-225, 237-243,  
256-262



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**FIGURE 55**

GTTGTGTCCTTCAGCAAAACAGTGGATTTAAATCTCCTTGCACAAGCTTGAGAGCAACAC  
AATCTATCAGGAAAGAAAGAAAGAAAAAACCGAACCTGACAAAAAGAAGAAAAAGAAG  
AAGAAAAAAATCATGAAAACCATCCAGCCAAAAATGCACAATTCTATCTCTTGGGCAAT  
CTTCACGGGGCTGGCTGCTCTGTGTCTCTTCCAAGGAGTGCCCGTGCGCAGCGGAGATGC  
CACCTTCCCCAAAGCTATGGACAACGTGACGGTCCGGCAGGGGGAGAGCGCCACCCTCAG  
GTGCACTATTGACAACCGGTCAACCGGGTGGCCTGGCTAAACCGCAGCACCATCCTCTA  
TGCTGGGAATGACAAGTGGTGCCTGGATCCTCGCGTGGTCCTTCTGAGCAACACCCAAAC  
GCAGTACAGCATCGAGATCCAGAACGTGGATGTGTATGACGAGGGCCCTTACACCTGCTC  
GGTGCAGACAGACAACCAACCCAAAGACCTCTAGGGTCCACCTCATTGTGCAAGTATCTCC  
CAAATTTGTAGAGATTTCTTCAGATATCTCCATTAATGAAGGGAACAATATTAGCCTCAC  
CTGCATAGCAACTGGTAGACCAGAGCCTACGGTTACTTGGAGACACATCTCTCCAAAGC  
GGTTGGCTTTGTGAGTGAAGACGAATACTTGGAAATTCAGGGCATCACCCGGGAGCAGTC  
AGGGGACTACGAGTGCAGTGCCTCCAATGACGTGGCCGCGCCCGTGGTACGGAGAGTAAA  
GGTCACCGTGAACCTATCCACCATACATTTTCAGAAGCCAAGGGTACAGGTGTCCCCGTGGG  
ACAAAAGGGGACACTGCAGTGTGAAGCCTCAGCAGTCCCCTCAGCAGAATTCCAGTGGTA  
CAAGGATGACAAAAGACTGATTGAAGGAAAGAAAGGGGTGAAAGTGGAAAACAGACCTTT  
CCTCTCAAACTCATCTTCTTCAATGTCTCTGAACATGACTATGGGAACTACACTTGCCT  
GGCCTCCAACAAGCTGGGCCACACCAATGCCAGCATCATGCTATTTGGTCCAGGCGCCGT  
CAGCGAGGTGAGCAACGGCACGTGAGGAGGGCAGGCTGCGTCTGGCTGCTGCCTCTTCT  
GGTCTTGCACCTGCTTCTCAAATTTTGATGTGAGTGCCACTTCCCCACCCGGGAAAGGCT  
GCCGCCACCACCACCACCAACACAACAGCAATGGCAACACCGACAGCAACCAATCAGATA  
TATACAAATGAAATTAGAAGAAACACAGCCTCATGGGACAGAAATTTGAGGGAGGGGAAC  
AAAGAATACTTTGGGGGGAAAAGAGTTTTTAAAAAAGAAATTGAAAATTGCCTTGCAGATA  
TTTAGGTACAATGGAGTTTTCTTTTCCCAAACGGGAAGAACACAGCACACCCGGCTTGGA  
CCCACTGCAAGCTGCATCGTGCAACCTCTTTGGTGCCAGTGTGGGCAAGGGCTCAGCCTC  
TCTGCCCACAGAGTGCCCCACGTGGAACATTCTGGAGCTGGCCATCCCAAATTCATCA  
GTCCATAGAGACGAACAGAATGAGACCTTCCGGCCCAAGCGTGGCGCTGCGGGCACTTTG  
GTAGACTGTGCCACCACGGCGTGTGTTGTGAAACGTGAAATAAAAAGAGCAAAAAAAA

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**FIGURE 56**

MKTIQPKMHNSISWAI FTGLAALCLFQGVPRSGDATFPKAMDNVTVRQGESATLRCTID  
NRVTRVAWLNRSTILYAGNDKWCLDPRVVLLSNTQTQYSIEIQNV DVYDEGPYTCSVQTD  
NHPKTSRVHLIVQVSPKIVEISSDISINEGNNISLT CIATGRPEPTVTWRHISPKAVGFV  
SEDEYLEIQGITREQSGDYEC SASNDVAAPVRRVKVT VNYPPYISEAKGTGVPVGQKGT  
LQCEASAVPSAEFQWKDDKRLIEGKKGVKVENRPFLSKLIFFNVSEHDYGN YTCVASNK  
LGHTNASIMLFGPGAVSEVSNGTSRRAGCVWLLPLLVLHLL LKF

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**FIGURE 57**

GCTGCGCCGGCTGCGGCTGCAGGGGAATCCGCTGTGGTGCGGCTGCCAGGCGCGGCCCT  
ACTCGAGTGGCTGGCGCGGGCGCGCTGCGCTCGGACGGCGCGTGCCAGGGGCCGCGGCG  
CCTGCGGGGCGAGGCTCTGGACGCCCTGCGGCCCTGGGACCTGCGCTGCCCTGGGGACGC  
GGCGCAGGAAGAGGAAGAGCTGGAAGAGCGGGCTGTGGCCGGGCCCCGCGCCCCTCCGCG  
CGGCCCTCCGCGCGGGCCCCGGGGAGGAGCGGGCAGTCGCGCCTTGCCCTCGCGCTGCGT  
GTGCGTCCCCGAGTCCCCGACACAGCAGCTGCGAGGGCTGCGGCCTGCAGGCGGTGCCCCG  
CGGCTTCCCCAGCGACACCCAGCTCCTGGACCTGAGGCGGAACCACTTCCCCTCGGTGCC  
CCGAGCGGCCTTCCCCGGNCTGGGCCACCTGGTGTGCTGCACCTGCAGCACTGCGGCAT  
CGCGGAGCTGGAAGCGGGCGCCCTGGCCGGGCTGGGCCGCTGATCTACCTGTACCTCTC  
CGACAACCAGCTCGCAGGCCTCAGCGCTGCTGCCCTTGAAGGGGCTCCCCGCTCGGCTA  
CCTGTACCTAGAACGCAACCGTTTCTGTCAGGTGCCAGGGGCTGCCNTGCGCGCCCTGCC  
CAGCCTCTTCTCCCTGCACCTGCAGGACAACGCTGTGGACCGCCTGGCACCTGGGGACCT  
GGGGAGAACACGGGCCTTGCGCTGGGTCTACCTGAGTGGAACCGCATCACCGAAGTGTC  
CCTTGGGGCGCTGGGCCAGCTCGGGAGCTGGAGAAGCTGCACCTGGACAGGAATCAGCT  
GCGAGAGGTGCCCACTGGGGCCTTGAGGGGCTGCCCTGCCCTCCTGGAGCTGCAGCTCTC  
GGGCAACCCACTCAGGGCCTTGCGTGACGGAGCCTTCCAGCCTGTGGGCAGGTGCTGCA  
GCACCTCTTCTGAACAGCAGTGGCCTGGAGCAGATTTGTCTTGGGGCCTTTTCAGGCCT  
GGGGCCCCGGGCTCCAGAGCCTGCACCTGCAGAAGAACCAGCTTCGGGCCCTGCCTGCCCT  
GCCCAGTCTCAGCCAGCTGGAGCTCATCGACCTCAGCAGCAATCCCTTCCCCTGTGACTG  
CCAGCTGCTTCCGCTGCACAGGTGGCTTACTGGGCTGAACCTGCGGGTGGGGGCCACCTG  
CGCCACCCCTCCCAATGCCCGTGGCCAGAGGGTGAAGGCTGCAGCTGCTGTCTTTGAAGA  
CTGCCCCGGGCTGGGCTGCCAGAAAGGCCAAGCGGACACCAGCCTCCAGGCCAGTGCCAG  
GAGAACCCCCATCAAAGGAAGACAGTGTGGAGCAGATAAGAACATCCTCTTCCCCACATG  
GTACCACACTGTGGAGCCCACCTCGCTGTCATAGGCCTGCGGCTCTGAAGGATGGCTTTG  
CCGCTCCCGCTCTGCCCCCTCAAGTGGAACCCAAGCTGGGCTCAGAATCTGTAGAGTGAG  
GCCCCACCAAGGGAAACGACACCCACGGCCTGAGAGCCAGGTGGAGTCCTGCCACTCAGC  
TGCCTGCCTTTGCTCCCACCCTCTCCACCCCTCAAAGAGGTCTCGAGGGGACACTCTGAA  
GGCACCTGGCTCAGAACCACTGCCATCCAAGGAGCGAGGAGTCCAGGGCTGAGCAAATG  
CAGCGGGGAGGTGCGCAGTCCCCCTGCTTCCCGATCCTCATTTTCTGCTTCACTTGACTC  
CTCCAGATAGGAGCTGCTCTCACTGCCACACTGCTG

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**FIGURE 58**

LRRLRLQGNPLWCGCQARPLLEWLLARARVRS DGACQGPRRLRGEALDALRPWDLRCPGDA  
AQEEEELEERAVAGPRAPPRGPPRGPGEEERAVAPCPACVCVPESRHSSCEGCGLQAVPR  
GFPSDTQLLDLRRNHFPSPRAAFPGLGHLVSLHLQHCGIAELEAGALAGLGRLIYLYLS  
DNQLAGLSAAALEGAPRLGYLYLERNRFLQVPGAAXRALPSLFSLHLQDNAVDRLAPGDL  
GRTRALRWVYLSGNRITEVSLGALGPARELEKLHLDRLNQLREVPTGALEGLPALLELQLS  
GNPLRALRDGA FQPVGRSLQHLFLNSSGLEQICPGAFSGLGPGQLSLHLQKNQLRALPAL  
PSLSQLELIDLSSNPFPCDCQLLPLHRWLTGLNLRVGATCATPPNARGQVRVKA AA AVFED  
CPGWAARKAKRTPASRPSARRTPIKGRQCGADKNILFPTWYHTVEPTSLS

**Signal sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

325-328

**Glycosaminoglycan attachment site:**

338-341

**Protein kinase C phosphorylation site:**

438-440

**N-myristoylation site:**

166-171, 186-191, 253-258, 286-291, 335-340, 339-344, 450-455

**Leucine rich repeat N-terminal domain:**

94-123

**Leucine Rich Repeat:**

125-148, 149-172, 173-196, 197-220, 221-244, 245-268, 269-292, 293-316, 318-341, 343-364, 365-386

**Leucine rich repeat C-terminal domain:**

374-422

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**FIGURE 59**

CTCCACGGTGTCCAGCGCCAGAAATGCGGCTTCTGGTCCTGCTATGGGGTTGCCTGCTG  
CTCCAGGTTATGAAGCCCTGGAGGGCCCAGAGGAAATCAGCGGGTTCGAAGGGGACACT  
GTGTCCCTGCAGTGCACCTACAGGGAAGAGCTGAGGGACCACCGGAAGTACTGGTGCAGG  
AAGGGTGGGATCCTCTTCTCTCGCTGCTCTGGCACCATCTATGCAGAAGAAGAAGGCCAG  
GAGACAATGAAGGGCAGGGTGTCCATCCGTGACAGCCGCCAGGAGCTCTCGCTCATTGTG  
ACCCTGTGGAACCTCACCTGCAAGACGCTGGGGAGTACTGGTGTGGGGTCGAAAAACGG  
GGCCCCGATGAGTCTTTACTGATCTCTCTGTTCTGTTCTTTCCAGGACCCTGCTGTCTCTCC  
TCCCTTCTCCCACCTTCCAGCCTCTGGCTACAACACGCCTGCAGCCCCAAGGCAAAAGCT  
CAGCAAACCCAGCCCCCAGGATTGACTTCTCCTGGGCTCTACCCGGCAGCCACCACAGCC  
AAGCAGGGGAAGACAGGGGCTGAGGCCCTCCATTGCCAGGGACTTCCAGTACGGGCAC  
GAAAGGACTTCTCAGTACACAGGAACCTCTCCTCACCAGCGACCTCTCCTCCTGCAGGG  
AGCTCCCCCCCCCATGCAGCTGGACTCCACCTCAGCAGAGGACACCAGTCCAGCTCTC  
AGCAGTGGCAGCTCTAAGCCCAGGGTGTCCATCCCGATGGTCCGCATACTGGCCCCAGTC  
CTGGTGTCTGCTGAGCCTTCTGTGAGCCGACGGCCTGATCGCCTTCTGCAGCCACCTGCTC  
CTGTGGAGAAAGGAAGCTCAACAGGCCACGGAGACACAGAGGAACGAGAAGTTCTGGCTC  
TCACGCTTGACTGCGGAGGAAAAGGAAGCCCCCTTCCAGGCCCTGAGGGGGACGTGATC  
TCGATGCCTCCCCCTCCACACATCTGAGGAGGAGCTGGGCTTCTCGAAGTTTGTCTCAGCG  
TAGGGCAGGAGGCCCTCCTGGCCAGGCCAGCAGTGAAGCAGTATGGCTGGCTGGATCAGC  
ACCGATTCCCCGAAAGCTTTCACCTCAGCCTCAGAGTCCAGCTGCCCGGACTCCAGGGCT  
CTCCCCACCCTCCCCAGGCTCTCCTCTTGCACTGTTCCAGCCTGACCTAGAAGCGTTTGTCT  
AGCCCTGGAGCCCAGAGCGGTGGCCTTGCTCTTCCGGCTGGAGACTGGGACATCCCTGAT  
AGGTTACATCCCTGGGCAGAGTACCAGGCTGCTGACCCTCAGCAGGGCCAGACAAGGCT  
CAGTGGATCTGGTCTGAGTTTCAATCTGCCAGGAACCTCCTGGGCCTCATGCCCAGTGTCTG  
GACCCTGCCTTCTCCTCCACTCCAGACCCACCTTGTCTTCCCTCCCTGGCGTCTCAGAC  
TTAGTCCCACGGTCTCCTGCATCAGCTGGTGATGAAGAGGAGCATGCTGGGGTGAGACTG  
GGATTCTGGCTTCTCTTTGAACCACCTGCATCCAGCCCTTCCAGGAAGCCTGTGAAAAACG  
TGATTCTGGCCCCACCAAGACCCACCAAAACCATCTCTGGGCTTGGTGCAGGACTCTGA  
ATTCTAACAATGCCCAGTGACTGTGCACTTGAGTTTGAGGGCCAGTGGGCCTGATGAAC  
GCTCACACCCCTTCCAGCTTAGAGTCTGCATTTGGGCTGTGACGTCTCCACCTGCCCAAT  
AGATCTGCTCTGTCTGCGACACCAGATCCACGTGGGGACTCCCCTGAGGCCTGCTAAGTC  
CAGGCCTTGGTGCAGGTGAGGTGCACATTGCAGGATAAGCCCAGGACCGGCACAGAAGTGG  
TTGCCTTTNCCATTGTGCCCTCCCTGNNCCATGCCTTCTTGCCCTTGGAAAAAATGATGAA  
GAAAACCTTGGCTCCTTCTTGTCTGGAAAGGGTTACTTGCCCTATGGGTTCTGGTGGCTA  
GAGAGAAAAGTAGAAAACCAGAGTGCACGTAGGTGTCTAACACAGAGGAGAGTAGGAACA  
GGGCGGATACCTGAAGGTGACTCCGAGTCCAGCCCCCTGGAGAAGGGGTGCGGGGTGGTG  
GTAAAGTAGCACAACTACTATTTTTTTTCTTTTCCATTATTATTGTTTTTTAAGACAGA  
ATCTCGTGTCTGCTGCCCAGGCTGGAGTGCAGTGGCACGATCTGCAAACCTCCGCCTCCTGG  
GTTCAAGTGATTCTTCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCACGCACCACC  
ACACCTGGCTAATTTTTGTACTTTTAGTAGAGATGGGGTTTACCATTGTTGGCCAGGCTG  
GTCTTGAACCTCTGACCTCAAATGAGCCTCCTGCTTCAGTCTCCCAAATTGCCGGGATTA  
CAGGCATGAGCCACTGTGTCTGGCCCTATTTCTTTTAAAAAGTGAAATTAAGAGTTGTTT  
AGTATGCAAACTTGGAAGATGGAGGAGAAAAAGAAAAGGAAGAAAAAATGTCACCCA  
TAGTCTCACCAGAGACTATCATTATTTCTGTTTGTGTTGTTTCTTCTTCCACTCTTTCTTC  
TTCACATAATTTGCCGGTGTCTTTTACAGAGCAATTATCTTGTATATACAACCTTTGTA  
TCCTGCCTTTTCCACCTTATCGTTCCATCACTTTATTCCAGCACTTCTCTGTGTTTTACA  
GACCTTTTTTATAAATAAAATGTTTCATCAGCTGCATAAAAAAAAAAAAAA

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**FIGURE 60**

MRLLVLLWGCLLLPGYEALLEGPEEISGFEGDTVSLQCTYREELRDHRKYWCRKGGILFSR  
CSGTIYAEEEGQETMKGRVSIRDSRQELSLIVTLWNLTLDAGEYWCGVEKRGPDSESLI  
SLFVFPGPCCPPSPSPPTFQPLATTRLQPKAKAQQTQPPGLTSPGLYPAATTAKQKGTGAE  
APPLPGTSQYGHERTSQYTGTSPHPATSPAGSSRPPMQLDSTSAEDTSPALSSGSSKPR  
VSIPMVRILAPVLVLLSLLSAAGLIAFCSHLLLRKEAQQATETQRNEKFWLSRLTAEK  
EAPSQAPEGDVISMPLHTSEEEELGFSKFVSA

**Important features:****Signal peptide:**

amino acids 1-17

**Transmembrane domain:**

amino acids 248-269

**N-glycosylation site:**

amino acids 96-99

**Fibrinogen beta and gamma chains C-terminal domain:**

amino acids 104-113

**Ig like V-type domain:**

amino acids 13-128

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**FIGURE 61**

CGGGCCAGCCTGGGGCGGCCGGCCAGGAACCAACCCGTTAAGGTGTCTTCTCTTTAGGGAT  
GGTGAGGTTGGAAAAAGACTCCTGTAACCCTCCTCCAGGATGAACCACCTGCCAGAAGAC  
ATGGAGAACGCTCTCACCGGGAGCCAGAGCTCCCATGCTTCTCTGCGCAATATCCATTCC  
ATCAACCCACACAACCTCATGGCCAGGATTGAGTCCATGAAGGAAGGGAAAAGAAAGGC  
ATATCTGATGTCAGGAGGACTTTCTGTTTGTGTTGTCACCTTTGACCTCTTATTCGTAACA  
TTACTGTGGATAATAGAGTTAAATGTGAATGGAGGCATTGAGAACACATTAGAGAAGGAG  
GTGATGCAGTATGACTACTATTCTTCATATTTTGGATATATTTCTTCTGGCAGTTTTTTCGA  
TTTAAAGTGTTAATACTTGCATATGCTGTGTGCAGACTGCGCCATTGGTGGGCAATAGCG  
TTGACAAACGGCAGTGACCAGTGCCTTTTTACTAGCAAAAGTGATCCTTTTCGAAGCTTTTC  
TCTCAAGGGGCTTTTGGCTATGTGCTGCCCATCATTTTCATTTCATCCTTGCCCTGGATTGAG  
ACGTGGTTCCCTGGATTTCAAAGTGTTACCTCAAGAAGCAGAAGAAGAAAACAGACTCCTG  
ATAGTTTCAGGATGCTTCAGAGAGGGCAGCACTTATACCTGGTGGTCTTTCTGATGGTCAG  
TTTTATTTCCCTCCTGAATCCGAAGCAGGATCTGAAGAAGCTGAAGAAAACAGGACAGT  
GAGAAACCACTTTTAGAACTATGAGTACTACTTTTGTAAATGTGAAAAACCTTCACAGA  
AAGTCATCGAGGCAAAAAGAGGCAGGCAGTGAGTCTCCCTGTCGACAGTAAAGTTGAAA  
TGGTGACGTCCACTGCTGGCTTTATTGAACAGCTAATAAAGATTTATTTATTGTAATACC  
TCACAAACGTTGTACCATATCCATGCACATTTAGTTGCCTGCCTGTGGCTGGTAAGGTAA  
TGTCATGATTCATCCTCTCTTCAGTGAGACTGAGCCTGATGTGTAAACAAATAGGTGAAG  
AAAGTCTTGTGCTGTATTCCTAATCAAAAGACTTAATATATTGAAGTAACACTTTTTTTAG  
TAAGCAAGATACCTTTTTTATTTCAATTCACAGAATGGAATTTTTTTTGTTCATGTCTCAG  
ATTTATTTTGTATTTCTTTTTTAACACTCTACATTTCCCTTGTTTTTTAACTCATGCACA  
TGTGCTCTTTGTACAGTTTTTAAAAAGTGTAATAAAATCTGACATGTCAATGTGGCTAGTT  
TTATTTTTCTTGTTTTGCATTATGTGTATGGCCTGAAGTGTTGGACTTGCAAAAGGGGAA  
GAAAGGAATTGCGAATACATGTAAAATGTCACCAGACATTTGTATTATTTTTATCATGAA  
ATCATGTTTTTCTCTGATTGTTCTGAAATGTTCTAAATACTCTTATTTTGAATGCACAAA  
ATGACTTAAACCATTCATATCATGTTTCCTTTGCGTTCAGCCAATTTCAATTAAAATGAA  
CTAAATTAAAAA

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**FIGURE 62**

MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVT  
FDLLFVTLLWIIELNVNGGIENTLEKEVMQYDYYSSYFDIFLLAVFRFKVLILAYAVCRL  
RHWWAIALTTAVTSAFLLAKVILSKLFSQGAFGYVLPPIISFILAWIETWFLDFKVLPOEA  
EEENRLLIVQDASERAALIPGGLSDGQFYSPPESEAGSEEAEKQDSEKPLLEL

**Important features of the protein:****Signal peptide:**

amino acids 1-20

**Transmembrane domains:**

amino acids 54-72, 100-118, 130-144, 146-166

**N-myristoylation sites:**

amino acids 14-20, 78-84, 79-85, 202-208, 217-223



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**FIGURE 63**

GCGCCGGGAGCCCATCTGCCCCAGGGGCACGGGGCGCGGGGCCGGCTCCCCGCCGGCAC  
ATGGCTGCAGCCACCTCGCGCGCACCCCGAGGCGCCGCGCCAGCTCGCCCCGAGGTCCGT  
CGGAGGCGCCCGGCCGCCCCGGAGCCAAGCAGCAACTGAGCGGGGAAGCGCCCGCGTCCG  
GGGATCGGGATGTCCTCCTCCTTCTCCTCTTGCTAGTTTCTTACTATGTTGGAACCTTG  
GGGACTCACACTGAGATCAAGAGAGTGGCAGAGGAAAAGGTCACTTTGCCCTGCCACCAT  
CAACTGGGGCTTCCAGAAAAAGACACTCTGGATATTGAATGGCTGCTCACCGATAATGAA  
GGGAACCAAAAAGTGGTGATCACTTACTCCAGTCGTATGTCTACAATAACTTGACTGAG  
GAACAGAAGGGCCGAGTGGCCTTTGCTTCCAATTTCTTGGCAGGAGATGCCTCCTTGACG  
ATTGAACCTCTGAAGCCAGTGATGAGGGCCGGTACACCTGTAAGGTTAAGAATTCAGGG  
CGCTACGTGTGGAGCCATGTCATCTTAAAAGTCTTAGTGAGACCATCCAAGCCCAAGTGT  
GAGTTGGAAGGAGAGCTGACAGAAGGAAGTGACCTGACTTTGCAGTGTGAGTCATCCTCT  
GGCACAGAGCCCATTTGTGTATTACTGGCAGCGAATCCGAGAGAAAGAGGGAGAGGATGAA  
CGTCTGCCTCCCAAATCTAGGATTGACTACAACCACCCTGGACGAGTTCTGCTGCAGAAT  
CTTACCATGTCTTACTCTGGACTGTACCACTGCACAGCAGGCAACGAAGCTGGGAAGGAA  
AGCTGTGTGGTGCGAGTAACTGTACAGTATGTACAAAGCATCGGCATGGTTGCAGGAGCA  
GTGACAGGCATAGTGGCTGGAGCCCTGCTGATTTTCTTCTTGGTGTGGCTGCTAATCCGA  
AGGAAAGACAAAGAAAGATATGAGGAAGAAGAGAGACCTAATGAAATTCGAGAAGATGCT  
GAAGCTCCAAAAGCCCGTCTTGTGAAACCCAGCTCCTCTTCTCAGGCTCTCGGAGCTCA  
CGCTCTGGTTCTTCTCCTCCTCCTCGCTCCACAGCAAATAGTGCCTCACGCAGCCAGCGGACA  
CTGTCAACTGACGCAGCACCCCAGCCAGGGCTGGCCACCCAGGCATACAGCCTAGTGGGG  
CCAGAGGTGAGAGGTTCTGAACCAAGAAAGTCCACCATGCTAATCTGACCAAAGCAGAA  
ACCACACCCAGCATGATCCCCAGCCAGAGCAGAGCCTTCCAAACGGTCTGAATTACAATG  
GACTTGACTCCCACGCTTTCTTAGGAGTCAGGGTCTTTGGACTCTTCTCGTCATTGGAGC  
TCAAGTCACCAGCCACACAACCAGATGAGAGGTATCTAAGTAGCAGTGAGCATTGCACG  
GAACAGATTGAGATGAGCATTCTTCTTATACAATACCAAACAAGCAAAAGGATGTAAGCT  
GATTCATCTGTAAAAGGCATCTTATTGTGCCTTTAGACCAGAGTAAGGGAAAGCAGGAG  
TCCAAATCTATTTGTTGACCAGGACCTGTGGTGAGAAGGTTGGGGAAAGGTGAGGTGAAT  
ATACCTAAAACCTTTTAATGTGGGATATTTTGTATCAGTGCTTTGATTCACAATTTTCAAG  
AGGAAATGGGATGCTGTTTGTAAATTTTCTATGCATTTCTGCAAACTTATTGGATTATTA  
GTTATTGAGACAGTCAAGCAGAACCCACAGCCTTATTACACCTGTCTACACCATGTACTG  
AGCTAACCACTTCTAAGAACTCCAAAAAAGGAAACATGTGTCTTCTATTCTGACTTAAC  
TTCATTTGTGATAAGGTTTGGATATTAATTTCAAGGGGAGTTGAAATAGTGGGAGATGGA  
GAAGAGTGAATGAGTTTCTCCCACTCTATACTAATCTCACTATTTGTATTGAGCCCCAAA  
TAACTATGAAAGGAGACAAAAATTTGTGACAAAGGATTGTGAAGAGCTTTCCATCTTCAT  
GATGTTATGAGGATTGTTGACAAACATTAGAAATATATAATGGAGCAATTGTGGATTTC  
CCTCAAATCAGATGCCCTCTAAGGACTTTCTTGCTAGATATTTCTGGAAGGAGAAAATACA  
ACATGTCATTTATCAACGTCCTTAGAAAGAATTCTTCTAGAGAAAAAGGGATCTAGGAAT  
GCTGAAAGATTACCCAACATAACCATTATAGTCTCTTCTTTCTGAGAAAATGTGAAACCAG  
AATTGCAAGACTGGGTGGACTAGAAAGGGAGATTAGATCAGTTTTCTTAAATATGTCAA  
GGAAGGTAGCCGGGCATGGTGCCAGGCACCTGTAGGAAAATCCAGCAGGTGGAGGTTGCA  
GTGAGCCGAGATTATGCCATTGCACTCCAGCCTGGGTGACAGAGCGGGACTCCGTCTC

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**FIGURE 64**

MSLLLLLLLLVSYYVGTLGTHTEIKRVAEEKVTLPCHHQLGLPEKDTLDIEWLLTDNEGNQ  
KVVITYSSRHVYNNLTTEEQGRVAFASNFLAGDASLQIEPLKPSDEGRYTCKVKNSGRYV  
WSHVILKVLVRPSKPKCELEGELTEGSDLTQCESSSGTEPIVYYWQRIREKEGEDERLP  
PKSRIDYNHPGRVLLQNLTMSYSGLYQCTAGNEAGKESCVVRVTVQYVQSIGMVAGAVTG  
IVAGALLIFLLVWLLIRRKDKERYEEEEERPNEIREDAEAPKARLVKPPSSSSSGSRSSRSG  
SSSTRSTANSASRSQRTLSTDAAPQPGLATQAYSLVGPEVRGSEPKKVHHANLTKAETTP  
SMIPSQSRAFQTV

**Signal sequence:**  
amino acids 1-16

**Transmembrane domain:**  
amino acids 232-251

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**FIGURE 65**

GTCTGGGGCTGCGCGACGGCGCAGGGGCTGCGGGGAGCGCCGCGCAGGCCGTGCAGTTCCT  
AGCGAGGAGGCGCCGCCGCGCCATTGCCGCTCTCTCGGTGAGCGCAGCCCCGCTCTCCGGGC  
CGGGCCTTCGCGGGCCACCGGCGCCATGGGGCCAGTGCGGCATCACCTCCTCCAAGACCGT  
GCTGGTCTTTCTCAACCTCATCTTCTGGGGGGCAGCTGGCATTATGCTATGTGGGAGC  
CTATGTCTTCATCACTTATGATGACTATGACCACTTCTTTGAAGATGTGTACACGCTCAT  
CCCTGCTGTAGTGATCATAGCTGTAGGAGCCCTGCTTTTCATCATTGGGCTAATTGGCTG  
CTGTGCCACAATCCGGGAAAGTCGCTGTGGACTTGCCACGTTTGTTCATCATCCTGCTCTT  
GGTTTTTGTTCACAGAAGTTGTTGTAGTGGTTTTGGGATATGTTTACAGAGCAAAGGTGGA  
AAATGAGGTTGATCGCAGCATTAGAAAGTGTATAAGACCTACAATGGAACCAACCTGA  
TGCTGCTAGCCGGGCTATTGATTATGTACAGAGACAGCTGCATTGTTGTGGAATTCACAA  
CTACTCAGACTGGGAAAATACAGATTGGTTCAAAGAAACCAAAAACCAGAGTGTCCCTCT  
TAGCTGCTGCAGAGAGACTGCCAGCAATTGTAATGGCAGCCTGGCCACCCTTCCGACCT  
CTATGCTGAGGGGTGTGAGGCTCTAGTAGTGAAGAAGCTACAAGAAATCATGATGCATGT  
GATCTGGGCCGCACCTGGCATTTCAGCTATTGAGCTGCTGGGCATGCTGTGTGCTTGCAT  
CGTGTGTGCAGAAGGAGTAGAGATCCTGCTTACGAGCTCCTCATCACTGGCGGAACCTA  
TGCATAGTTGACAACCTCAAGCCTGAGCTTTTTGGTCTTGTCTGATTTGGAAGGTGAATT  
GAGCAGGTCTGCTGCTGTTGGCCTCTGGAGTTCATTTAGTTAAAGCACATGTACACTGGT  
GTTGGACAGAGCAGCTTGGCTTTTCATGTGCCACCTACTTACCTACTACCTGCGACTTT  
CTTTTTCTTGTCTAGCTGACTCTTCATGCCCCTAAGATTTTAAGTACGATGGTGAACG  
TTCTAATTTCAGAACCAATTGCGAGTCATGTAGTGTGGTAGAATTAAAGGAGGACACGAG  
CCTGCTTCTGTTACCTCCAAGTGGTAACAGGACTGATGCCGAAATGTCACCAGGTCTTTT  
CAGTCTTCACAGTGGAGAACTCTTGGCCAAAGTTTTTTCGGGGAGGAGGAGGAAACCAG  
CTTTCTGGTTAAGGTTAACACCAGATGGTGCCCTCATTTGGTGTCTTTTAAAAAATATT  
TACTGTAGTCCAATAAGATAGCAGCTGTACAAAATGACTAAAATAGATTGTAGGATCATA  
TGGCGTATATCTTGGTTTCATCTTCAAAATCAGAGACTGAGCTTTGAACTAGTGGTTTTT  
AATCAAAGTTGGCTTTATAGGAGGAGTATAATGTATGCACTACTGTTTTAAAGAATTAG  
TGTGAGTGTGTTTTTGTATGAATGAGCCCATTCATGGTAAGTCTTAAGCTTGTGGAAAT  
AATGTACCCATGTAGACTAGCAAAATAGTATGTAGATGTGATCTCAGTTGTAAATAGAAA  
AATCTAATTCAATAAACTCTGTATCAGCCCCCAAAAAAAAAAAAAAAAAA

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**FIGURE 66**

MGQCGITSSKTVLVFLNLI FWGAAGILCYVGAYVFITYDDYDHFFEDVYTLIPAVVIIAV  
GALLFIIGLIGCCATIRESRCGLATFVIIILLVFVTEVVVVVLGYVYRAKVENEVDRSIQ  
KVYKTYNGTNPDAASRAIDYVQRQLHCCGIHNYSDWENTDWFKETKNQSVPLSCCRETAS  
NCNGSLAHPSDLYAEGCEALVVKKLQEIMMHVIWAALAFAAIQLLGMLCACIVLCRRSRD  
PAYELLITGGTYA

**Signal peptide:**

none

**Type II transmembrane domain:**

11-38

**Other transmembrane domains:**

48-68, 87-107, 208-235

**N-glycosylation site:**

127-131, 152-156, 167-171, 183-187

**Tyrosine kinase phosphorylation site:**

236-244

**N-myristoylation site:**

5-11, 68-74, 71-77, 226-232

**Prokaryotic membrane lipoprotein lipid attachment site:**

62-73, 221-232

**Transmembrane 4 family proteins:**

7-35, 56-106

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**FIGURE 67**

GCGGCACCTGGAAGATGCGCCCATTTGGCTGGTGGCCTGCTCAAGGTGGTGTTCGTGGTCT  
TCGCCTCCTTGTGTGCCTGGTATTCGGGGTACCTGCTCGCAGAGCTCATTCCAGATGCAC  
CCCTGTCCAGTGCTGCCTATAGCATCCGCAGCATCGGGGAGAGGCCTGTCCTCAAAGCTC  
CAGTCCCCAAAAGGCAAAAATGTGACCACTGGACTCCCTGCCCATCTGACACCTATGCCT  
ACAGGTTACTCAGCGGAGGTGGCAGAAGCAAGTACGCCAAAATCTGCTTTGAGGATAACC  
TACTTATGGGAGAACAGCTGGGAAATGTTGCCAGAGGAATAAACATTGCCATTGTCAACT  
ATGTAACCTGGGAATGTGACAGCAACACGATGTTTTGATATGTATGAAGGCGATAACTCTG  
GACCGATGACAAAGTTTTATTTCAGAGTGCTGCTCCAAAATCCCTGCTCTTCATGGTGACCT  
ATGACGACGGAAGCACAAGACTGAATAACGATGCCAAGAATGCCATAGAAGCACTTGGAA  
GTAAAGAAATCAGGAACATGAAATTCAGGTCTAGCTGGGTATTTATTGCAGCAAAGGCT  
TGGAACCTCCCTTCCGAAATTCAGAGAGAAAAGATCAACCACTCTGATGCTAAGAACACA  
GATATTCTGGCTGGCCTGCAGAGATCCAGATAGAAGGCTGCATACCCAAAGAACGAAGCT  
GACTGTCAGGGTCCTGAGTAAATGTGTTCTGTATAAAACAAATGCAGCTGGAATCGCTCA  
AGAATCTTATTTTTCTAAATCCAACAGCCCATATTTGATGAGTATTTTGGGTTTGTTGTA  
AACCAATGAACATTTGCTAGTTGTATCAAATCTTGGTACGCAGTATTTTATACCAGTAT  
TTTATGTAGTGAAGATGTCAATTAGCAGGAACTAAAATGAATGGAAATCTTAAAAAAA  
AAA

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**FIGURE 68**

MRPLAGGLLKVVVFVVFASLCAWYSGYLLAELIPDAPLSSAAYSIRSIGERPVLKAPVPKR  
QKCDHWTPCPSDTYAYRLLSGGGRSKYAKICFEDNLLMGEQLGNVARGINIAIVNYVTGN  
VTATRCFDMYEGDNSGPMTKFIQSAAPKSLLFMVTYDDGSTRLNNDKNAIEALGSKEIR  
NMKFRSSWVFIAAKGLELPSEIQREKINHSDAKNNRYSGWPAEIQIEGCI PKERS

**Signal sequence:**

amino acids 1-20

**N-glycosylation sites:**

amino acids 120-124, 208-212

**Glycosaminoglycan attachment site:**

amino acids 80-84

**N-myristoylation sites:**

amino acids 81-87, 108-114, 119-125

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**FIGURE 69**

ACACAACTTTACACCTGAATGAACGCCAAACCTCTATGGATATATAAAGGGAAGCTTGAG  
GAGGAATTTACAGTTACAGTGCAGAAGCAGAAGCAAAAGAATTAACCAGCTCTTCAGTC  
AAGCAAATCCTCTACTCACCATGCCTTCCTCCTGCCATTCATTTCTATCTCCTTCCCCTTG  
CATGCATCCTAATGAAAAGCTGTTTGGCTTTTAAAAATGATGCCACAGAAATCCTTTATT  
CACATGTGGTTAAACCTGTTCCAGCACACCCAGCAGCAACAGCACGTTGAATCAAGCCA  
GAAATGGAGGCAGGCATTTTCACTAACACTGGACTGGATCGGAACACTCGGGTTCAAGTGG  
GTTGCCGGGAAGTGCCTTCCACCAAATACATCTCTGATGGCCAGTGCACCAGCATCAGCC  
CTCTGAAGGAGCTGGTGTGTGCTGGCGAGTGCTTGCCCCTGCCAGTGCTCCCTAACTGGA  
TTGGAGGAGGCTATGGAACAAAGTACTGGAGCAGGAGGAGCTCCCAGGAGTGGCGGTGTG  
TCAATGACAAAACCCGTACCCAGAGAATCCAGCTGCAGTGCCAAGATGGCAGCACACGCA  
CCTACAAAATCACAGTAGTCACTGCCTGCAAGTGCAAGAGGTACACCCGGCAGCACAAACG  
AGTCCAGTCACAACTTTGAGAGCATGTACCTGCCAAGCCAGTCCAGCATCACAGAGAGC  
GGAAAAGAGCCAGCAAATCCAGCAAGCACAGCATGAGTTAGAACTCAGACTCCCATAACT  
AGACTTACTAGTAACCATCTGCTTTACAGATTTGATTGCTTGGAAGACTCAAGCCTGCCA  
CTGCTGTTTTCTCACTTGAAAGTATATGCTTTCTGCTTTGATCAAACCCAGCAAGCTGTC  
TTAAGTATCAGGACCTTCTTTGGGAATAGTTTTTCTTTTAAAGTTTTTCAAGATGTAGG  
TATATCCATGAATGCAATTTGCATTTAAATTCACGTATCCCTGTAGTTTTAAATTCCTCA  
TTGGTCTTAAAAGACTGTTGATACTATAAACATCAGTGGAATCAATTATATTTTAAACA  
GAAAAGGGCTT

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**FIGURE 70**

MLPPAIHFYLLPLACILMKSCLA FKNDATEILYSHVVKPVP AHPSSNSTLNQARNGGRHF  
SNTGLDRNTRVQVGCRELRSTKYISDGQCT SISPLKELVCAGECLPLPVL PNWIGGGYGT  
KYWSRRSSQEWRCVNDKTRTQRIQLQCQDGSTR TYKITVVTACKCKRYTRQHNESSHNFE  
SMSPAKPVQHHRRERKRASKSSKHSMS

**Signal sequence:**

1-23

**Transmembrane domain:**

None

**N-glycosylation site:**

47-50, 173-176

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

125-128, 166-169, 195-198

**N-myristoylation site:**

64-69, 87-92, 115-120, 116-121, 150-155



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**FIGURE 71**

CCCAGGCTCTAGTGCAGGAGGAGAAGGAGGAGGAGCAGGAGGTGGAGATTCCCAGTTAAA  
AGGCTCCAGAATCGTGTACCAGGCAGAGAACTGAAGTACTGGGGCCTCCTCCACTGGGTC  
CGAATCAGTAGGTGACCCCGCCCCTGGATTCTGGAAGACCTCACCATGGGACGCCCCCGA  
CCTCGTGCGGCCAAGACGTGGATGTTCTGCTCTTGCTGGGGGGAGCCTGGGCAGGACAC  
TCCAGGGCACAGGAGGACAAGGTGCTGGGGGGTTCATGAGTGCCAACCCCATTCGCAGCCT  
TGGCAGGCGGCCTTGTTCCAGGGCCAGCAACTACTCTGTGGCGGTGTCCTTGTAAGGTGGC  
AACTGGGTCCTTACAGCTGCCCCACTGTAAAAAACCGAAATACACAGTACGCCTGGGAGAC  
CACAGCCTACAGAATAAAGATGGCCCAGAGCAAGAAATACCTGTGGTTTCAGTCCATCCCA  
CACCCCTGCTACAACAGCAGCGATGTGGAGGACCACAACCATGATCTGATGCTTCTTCAA  
CTGCGTGACCAGGCATCCCTGGGGTCCAAAGTGAAGCCCATCAGCCTGGCAGATCATTGC  
ACCCAGCCTGGCCAGAAGTGCACCGTCTCAGGCTGGGGCACTGTCAACAGTCCCCGAGAG  
AATTTTCTTGACACTCTCAACTGTGCAGAAGTAAAAATCTTTCCCCAGAAGAAGTGTGAG  
GATGCTTACCCGGGGCAGATCACAGATGGCATGGTCTGTGCAGGCAGCAGCAAAGGGGCT  
GACACGTGCCAGGGCGATTCTGGAGGCCCCCTGGTGTGTGATGGTGCCTCCAGGGCATC  
ACATCCTGGGGCTCAGACCCCTGTGGGAGGTCCGACAAACCTGGCGTCTATACCAACATC  
TGCCGCTACCTGGACTGGATCAAGAAGATCATAGGCAGCAAGGGCTGATTCTAGGATAAG  
CACTAGATCTCCCTTAATAAACTCACAACCTCTCTGGTTC

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**FIGURE 72**

MGRPRPRAAKTWMFLLLLGGAWAGHSRAQEDKVLGGHECQPHSQPWQAALFQGQQLLCGG  
VLVGGNWLTAAHCKKPKYTVRLGDHSLQNKDGPEQEIPVVQSIHPHCYNSSDVEDHNHD  
LMLLQLRDQASLGSKVKPISLADHCTQPGQKCTVSGWGTVTSPRENF PDTLNCAEVKIFP  
QKKCEDAYPGQITDGMVCAGSSKGADTCQGDSSGGLVCDGALQGITSWGS DPCGRSDKPG  
VYTNICRYLDWIKKIIGSKG

**Important Features:****Signal peptide:**

amino acids 1-23

**Transmembrane domain:**

amino acids 51-71

**N-glycosylation site:**

amino acids 110-113

**Serine proteases, trypsin family, histidine active site:**

amino acids 69-74 and 207-217

**Tyrosine kinase phosphorylation site:**

amino acids 182-188

**Kringle domain proteins motif:**

amino acids 205-217

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**FIGURE 73**

CTCGGGCGCGCACAGGCAGCTCGGTTTGCCTTGCGATTGAGCTGCGGGTCGCGGCCGGCG  
CCGGCCTCTCCAATGGCAAATGTGTGTGGCTGGAGGCGAGCGCGAGGCTTTCGGCAAAGG  
CAGTCGAGTGTTTGCAGACCGGGGCGAGTCTGTGAAAGCAGATAAAAGAAAACATTTAT  
TAACGTGTCATTACGAGGGGAGCGCCCGGGCGGGGCTGTCGCACTCCCCGCGGAACATTT  
GGCTCCCTCCAGCTCCGAGAGAGGAGAAGAAGAAAGCGGAAAAGAGGCAGATTACGTCG  
TTTCCAGCCAAGTGGACCTGATCGATGGCCCTCCTGAATTTATCACGATATTTGATTTAT  
TAGCGATGCCCCCTGGTTTGTGTGTTACGCACACACACGTGCACACAAGGCTCTGGCTCG  
CTTCCCTCCCTCGTTTCCAGCTCCTGGGCGAATCCCACATCTGTTTCAACTCTCCGCCGA  
GGGCGAGCAGGAGCGAGAGTGTGTGCAATCTGCGAGTGAAGAGGGACGAGGGAAAAGAAA  
CAAAGCCACAGACGCAACTTGAGACTCCCGCATCCCAAAGAAGCACCAGATCAGCAAAA  
AAAGAAGATGGGGCCCCCGAGCCTCGTGCTGTGCTTGCTGTCCGCAACTGTGTTCTCCCT  
GCTGGGTGGAAGCTCGGCCTTCTGTGCGACCACCGCCTGAAAGGCAGGTTTTCAGAGGGA  
CCGCAGGAACATCCGCCCCAACATCATCTGGTGCTGACGGACGACCAGGATGTGGAGCT  
GGGTTCCATGCAGGTGATGAACAAGACCCGGCGCATCATGGAGCAGGGCGGGGCGCACTT  
CATCAACGCCTTCGTGACCACACCCATGTGCTGCCCTCACGCTCCTCCATCCTCACTGG  
CAAGTACGTCCACAACCACAACCTACACCAACAATGAGAACTGCTCCTCGCCCTCCTG  
GCAGGCACAGCACGAGAGCCGCACCTTTGCCGTGTACCTCAATAGCACTGGCTACCGGAC  
AGCTTTCTTCGGGAAGTATCTTAATGAATAACAACGGCTCCTACGTGCCACCCGGCTGGAA  
GGAGTGGGTGGACTCCTTAAAACTCCCGCTTTTATACTACACGCTGTGTGCGAACGG  
GGTGAAAGAGAAGCACGGCTCCGACTACTCCAAGGATTACCTCACAGACCTCATCACCAA  
TGACAGCGTGAGCTTCTTCCGCACGTCCAAGAAGATGTACCCGCACAGGCCAGTCCTCAT  
GGTCATCAGCCATGCAGCCCCCACGGCCCTGAGGATTCAGCCCCACAATATTCAGGCCT  
CTTCCCAAACGCATCTCAGCACATCAGCCGAGCTACAATACTACGCGCCCAACCCGGACAA  
ACACTGGATCATGCGCTACACGGGGCCCATGAAGCCCATCCACATGGAATTCACCAACAT  
GCTCCAGCGGAAGCGCTTGACAGCCCTCATGTGCGGTGGACGACTCCATGGAGACGATTTA  
CAACATGCTGGTTGAGACGGGCGAGCTGGACAACACGTACATCGTATACACCGCCGACCA  
CGGTTACCACATCGGCCAGTTTGGCCTGGTGAAAGGGAAATCCATGCCATATGAGTTTGA  
CATCAGGGTCCCGTTCTACGTGAGGGGCCCCAACGTGGAAGCCGGCTGTCTGAATCCCCA  
CATCGTCTCAACATTGACCTGGCCCCCACCATCCTGGACATTGCAGGCCTGGACATACC  
TGCGGATATGGACGGGAAAATCCATCCTCAAGCTGCTGGACACGGAGCGGCCGGTGAATCG  
GTTTCACTTGAAAAAGAAGATGAGGGTCTGGCGGGACTCCTTCTTGGTGGAGAGAGGCAA  
GCTGCTACACAAGAGAGACAATGACAAGGTGGACGCCAGGAGGAGAACTTTCTGCCCAA  
GTACCAGCGTGTGAAGGACCTGTGTGACGCTGCTGAGTACCAGACGGCGTGTGAGCAGCT  
GGGACAGAAGTGGCAGTGTGTGGAGGACGCCACGGGGAAGCTGAAGCTGCATAAGTGCAA  
GGGCCCCATGCGGCTGGGCGGCAGCAGAGCCCTCTCCAACCTCGTGCCCAAGTACTACGG  
GCAGGGCAGCGAGGCCTGCACCTGTGACAGCGGGGACTACAAGCTCAGCCTGGCCGACG  
CCGGA AAAA ACTCTTCAAGAAGAAGTACAAGGCCAGCTATGTCCGCACTGCTCCATCCG  
CTCAGTGGCCATCGAGGTGGACGGCAGGGTGTACCACGTAGGCCTGGGTGATGCCGCCA  
GCCCCGAAACCTCACCAAGCGGCACTGGCCAGGGGCCCCCTGAGGACCAAGATGACAAGGA  
TGGTGGGGACTTCAGTGGCACTGGAGGCCTTCCCGACTACTCAGCCGCCAACCCCATTA  
AGTGACACATCGGTGCTACATCCTAGAGAACGACACAGTCCAGTGTGACCTGGACCTGTA  
CAAGTCCCTGCAGGCCTGGAAAGACCACAAGCTGCACATCGACCACGAGATTGAAACCT  
GCAGAACAAAATTAAGAACCTGAGGGAAGTCCGAGGTCACCTGAAGAAAAAGCGGCCAGA  
AGAATGTGACTGTACAAAAATCAGCTACCACACCCAGCACAAAGGCCGCTCAAGCACAG  
AGGCTCCAGTCTGCATCCTTTCAGGAAGGGCCTGCAAGAGAAGGACAAGGTGTGGCTGTT  
GCGGGAGCAGAAGCGCAAGAAGAACTCCGCAAGCTGCTCAAGCGCCTGCAGAACACGA  
CACGTGCAGCATGCCAGGCCTCACGTGCTTACCCACGACAACAGCACTGGCAGACGGC

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GCCTTTCTGGACACTGGGGCCTTTCTGTGCCTGCACCAGCGCCAACAATAACACGTACTG  
GTGCATGAGGACCATCAATGAGACTCACAATTCCTCTTCTGTGAATTTGCAACTGGCTT  
CCTAGAGTACTTTGATCTCAACACAGACCCCTACCAGCTGATGAATGCAGTGAACACACT  
GGACAGGGATGTCCCTCAACCAGCTACACGTACAGCTCATGGAGCTGAGGAGCTGCAAGGG  
TTACAAGCAGTGTAACCCCCGGACTCGAAACATGGACCTGGATGGAGGAAGCTATGAGCA  
ATACAGGCAGTTTCAGCGTCGAAAGTGGCCAGAAATGAAGAGACCTTCTTCCAAATCACT  
GGGACAACTGTGGGAAGGCTGGGAAGGTTAAGAAAACAACAGAGGTGGACCTCCAAAAACA  
TAGAGGCATCACCTGACTGCACAGGCAATGAAAAACCATGTGGGTGATTTCCAGCAGACC  
TGTGCTATTGGCCAGGAGGCCTGAGAAAGCAAGCACGCACTCTCAGTCAACATGACAGAT  
TCTGGAGGATAACCAGCAGGAGCAGAGATAACTTCAGGAAGTCCATTTTTTGCCCTGCTT  
TTGCTTTGGATTATACCTCACCAGCTGCACAAAATGCATTTTTTTCGTATCAAAAAGTCAC  
CACTAACCCTCCCCAGAAGCTCACAAAGGAAAACGGAGAGAGCGAGCGAGAGAGATTTT  
CTTGGAATTTCTCCCAAGGGCGAAAGTCATTGGAATTTTAAATCATAGGGGAAAAGCA  
GTCCTGTTCTAAATCCTCTTATTCTTTTGGTTTGTACAAAGAAGGAACCTAAGAAGCAGG  
ACAGAGGCAACGTGGAGAGGCTGAAAACAGTGCAGAGACGTTTGACAATGAGTCAGTAGC  
ACAAAAGAGATGACATTTACCTAGCACTATAAACCCCTGGTTGCCTCTGAAGAACTGCCT  
TCATTGTATATATGTGACTATTTACATGTAATCAACATGGGAACTTTTAGGGGAACCTAA  
TAAGAAATCCCAATTTTCAGGAGTGGTGGTGTCAATAAACGCTCTGTGGCCAGTGTA  
AAAAA

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**FIGURE 74**

MGPPSLVLCLLSATVFSLLGGSSAFLSHHRLKGRFQDRRNIRPNIILVLTDDQDVELGS  
MQVMNKTRRIMEQGAHFINAFVTTMCCPSRSSILTGKYVHNHNTYTNNECSPSWQA  
QHESRTFAVYLNSTGYRTAFFGKYLNEYNGSYVPPGWKEWVGLLKNSRFYNYTLCRNGVK  
EKHGSDYSKDYLTDLITNDSVSFFRTSKKMPHRPVLVISHAAPHGPEDSAPQYSRLFP  
NASQHITPSYNYAPNPDKHWIMRYTGPMKPIHMEFTNMLQKRQLQTLMSVDDSMETIYNM  
LVETGELDNTYIVYTADHGYHIGQFGLVKGKSMPEYFDIRVPFYVRGPNVEAGCLNPHIV  
LNIDLAPTILDIAGLDIPADM DGKSILKLLDTERPVNRFHLKKKMRVWRDSFLVERGKLL  
HKRDNDKVDAQEENFLPKYQRVKDLQRAEYQTACEQLGQKWQCVEDATGKLKLHKCKGP  
MRLGGSRALSNLVPKYQGQSEACTCDSDYKLSLAGRRKKLFKKKYKASYVRSRSIRSV  
AIEVDGRVYHVGLGDAAPRNLTKRHWPGAPEDQDDKDGGDFSGTGGLPDYSAANPIKVT  
HRCYILENDTVQCDLDLYKSLOAWKDHKLHIDHEIETLQNKIKNLREVRGHLKKKRPEEC  
DCHKISYHTQHKGRCLKHRGSSLHPFRKGLQEKDKVWLLREQKRKKKLRLKLLKRLQNNDTC  
SMPGLTCFTHDNQHWQTAPFWTLGPFCACTSANNTYWCMTINETHNFLFCEFATGFLE  
YFDLNTDPYQLMNAVNTLDRDVLNQLHVQLMELRSCGYKQCNPRTNMDLDGGSYEQYR  
QFQRRKWPEMKRPSSKSLGQLWEGWEG

**Important features:****Signal peptide:**

amino acids 1-17

**Sulfatases signature 1:**

amino acids 86-99

**Homologous region to sulfatase:**

amino acids 87-106, 133-146, 216-229, 291-320, 365-375

**N-glycosylation sites:**amino acids 65-69, 112-116, 132-136, 149-153, 171-175,  
198-202, 241-245, 561-565, 608-612, 717-721, 754-758,  
764-768

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**FIGURE 75**

CCCACGCGTCCGCCCACGCGTCCGGTGGACTATGGGCCAGTTTTTGTGCAAGAACCAGAT  
GATATTATTTTTTCCAAGTCTGATGAAAAGAAGGTAGCATTGAATTGTGAAGTTCGT  
GGCAATCCAGTTCACAGATGGCTTCGAAATGGAACAGAAATAGATCTGGAAAGT  
GATTATCGCTACAGTTTGATAGATGGCACCTTCATTATAAGCAATCCAAGTGAAGCAAAG  
GATTCTGGTCATTATCAGTGTTTAGCAACCAACACTGTGGGGAGTATTCTTAGTAGAGAA  
GCTACACTGCAGTTTGCCTATCTGGGAAATTTTAGTGGCCGACAAGAAGTGCAGTCTCT  
GTGAGGGAAGGCCAGGGTGTCTGATGCTCTCCTCCGCCACATTCACCAGAGATC  
ATCTATAGCTGGGTATTTAATGAGTTCCTTCCTTTGTGGCGGAAGACAGCCGCGGTTC  
ATCTCCCAGGAGACAGGCAACCTTTATATTTCTAAAGTCAAACATCAGATGTTGGCAGC  
TATATTTGTCTGGTGAAAAACACAGTGACGAATGCTAGAGTCCTTAGTCCTCCAACGCCA  
CTCACTCTGCGTAATGATGGTGTGATGGGAGAATATGAGCCGAAAATTGAGGTCCATTTT  
CCTTTACGGTTACAGCTGCTAAAGGAACAACCTGTTAAGATGGAATGCTTTGCACTTGGC  
AACCCCGTTCCAACAATCACATGGATGAAGGTTAATGGTTATATTCTAGTAAGGCACGT  
CTGCGGAAATCTCAGGCGGTGCTGGAAATACCGAATGTACAGCTGGATGATGCAGGCATT  
TATGAGTGCAGAGCTGAAAACCTCAGTGGAATAATTCCTTTCGTGGACAATTACAAGTA  
TACACCTACCCACACTGGGTAGAAAACTGAATGATACTCAGTTAGACAGTGGGAGCCCT  
CTCCGATGGGAATGTAAGGCTACTGGAAAACCCAGACCCACGTATCGTTGGCTGAAGAAT  
GGAGTACCCCTCTCACCTCAGAGTAGGGTTGAGATGGTTAATGGAGTATTGATGATCCAC  
AATGTGAATCAATCAGATGCTGGAATGTATCAGTGTTTGGCTGAAAATAAGTATGGAGCC  
ATTTACGCTAGTGCTGAGCTGAAGATTCTAGCTTCAGCTCCCACTTTTGCAGTGAATCAA  
CTGAAGAAAACAATAATTGTTACCAAAGACCAAGAAGTTGTCATAGAGTGCAAACCCCAA  
GGCTCTCCAAAACCAACCATCTCTTGGAAGAAAGGAGACAGAGCAGTTAGAGAAAACAAA  
AGAATAGCTATTCTTCCAGACGGGAGTCTACGGATCCTAAATGCTTCCAAATCAGACGAG  
GGAAAGTACGTTTGCCGAGGGGAAAACGTCTTTGGTTCTGCTGAAAT

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**FIGURE 76**

MCSPPPHSPEIIYSWVFNEFPSFVAEDSRRFISQETGNLYISKVQTSADVGSYICLVKNTV  
TNARVLSPTPLTLRNDGVMGEYEPKIEVHFPTVTAAGTTVKMECFALGNPVPTITWM  
KVNGYIPSKARLRKSQAVLEIPNVQLDDAGIYECRAENSRGKNSFRGQLQVYTYPHWVEK  
LNDTQLDSGSPLRWECKATGKPRPTYRWLKNGVPLSPQSRVEMVNGVLMIHNVNQSDAGM  
YQCLAENKYGAIYASAELKILASAPTFALNQLKKTIIIVTKDQEVVIECKPQGSPKPTISW  
KKGDRAVRENKRIAILPDGSLRILNASKSDEGKYVCRGENVFGSAE

**Signal sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

182-185, 234-237, 325-328

**Tyrosine kinase phosphorylation site:**

328-334

**N-myristoylation site:**

50-55, 150-155, 239-244, 250-255

**Immunoglobulin domain:**

2-56, 100-156, 189-245, 281-338

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**FIGURE 77**

GCTCCCAGCCAAGAACCCTCGGGGCCGCTGCGCGGTGGGGAGGAGTTCCCCGAAACCCGGC  
CGCTAAGCGAGGCCTCCTCCTCCCGCAGATCCGAACGGCCTGGGCGGGGTACCCCCGGCT  
GGGACAAGAAGCCGCCGCTGCCTGCCCGGGCCCGGGAGGGGGCTGGGGCTGGGGCCGG  
AGGCGGGGTGTGAGTGGGTGTGTGCGGGGGGCGGAGGCTTGATGCAATCCCGATAAGAAA  
TGCTCGGGTGTCTTGGGCACCTACCCGTGGGGCCCGTAAGGCGCTACTATATAAGGCTGC  
CGGCCCGGAGCCGCCGCGCCGTGAGAGCAGGAGCGCTGCGTCCAGGATCTAGGGCCACGA  
CCATCCCAACCCGGCACTCACAGCCCCGCAGCGCATCCCGGTGCGCCGCCAGCCTCCCCG  
ACCCCCATCGCCGGAGCTGCGCCGAGAGCCCCAGGGAGGTGCCATGCGGAGCGGGTGTGT  
GGTGGTCCACGTATGGATCCTGGCCGGCCTCTGGCTGGCCGTGGCCGGGCGCCCCCTCGC  
CTTCTCGGACGCGGGGCCCCACGTGCACTACGGCTGGGGCGACCCCATCCGCCTGCGGCA  
CCTGTACACCTCCGGCCCCCACGGGCTCTCCAGCTGCTTCCTGCGCATCCGTGCCGACGG  
CGTCGTGGACTGCGCGCGGGGCCAGAGCGCGCACAGTTTGCTGGAGATCAAGGCAGTCGC  
TCTGCGGACCGTGGCCATCAAGGGCGTGACAGCGTGCGGTACCTCTGCATGGGCGCCGA  
CGGCAAGATGCAGGGGCTGCTTCAGTACTCGGAGGAAGACTGTGCTTTCGAGGAGGAGAT  
CCGCCCAGATGGCTACAATGTGTACCGATCCGAGAAGCACCGCCTCCCGGTCTCCCTGAG  
CAGTGCCAAACAGCGGCAGCTGTACAAGAACAGAGGCTTTCTTCCACTCTCTCATTTCT  
GCCCATGCTGCCATGGTCCCAGAGGAGCCTGAGGACCTCAGGGGCCACTTGGAATCTGA  
CATGTTCTCTTCGCCCCCTGGAGACCGACAGCATGGACCCATTTGGGCTTGTCACCGGACT  
GGAGGCCGTGAGGAGTCCAGCTTTGAGAAGTAACTGAGACCATGCCCGGGCCTCTTCAC  
TGCTGCCAGGGGCTGTGGTACCTGCAGCGTGGGGGACGTGCTTCTACAAGAACAGTCCTG  
AGTCCACGTTCTGTTTAGCTTTAGGAAGAAACATCTAGAAGTTGTACATATTCAGAGTTT  
TCCATTGGCAGTGCCAGTTTCTAGCCAATAGACTTGTCTGATCATAACATTGTAAGCCTG  
TAGCTTGCCCAGCTGCTGCCTGGGCCCCCATTTCTGCTCCCTCGAGGTTGCTGGACAAGCT  
GCTGCACTGTCTCAGTTCTGCTTGAATACCTCCATCGATGGGGAACTCACTTCCTTTGGA  
AAAATTCTTATGTCAAGCTGAAATTCTCTAATTTTTTCTCATCACTTCCCCAGGAGCAGC  
CAGAAGACAGGCAGTAGTTTTAATTTTCAAGAACAGGTGATCCACTCTGTAAACAGCAGG  
TAAATTTCACTCAACCCCATGTGGGAATTGATCTATATCTCTACTTCCAGGGACCATTG  
CCCTTCCCAAATCCCTCCAGGCCAGAACTGACTGGAGCAGGCATGGCCCACCAGGCTTCA  
GGAGTAGGGGAAGCCTGGAGCCCCACTCCAGCCCTGGGACAACCTTGAGAATTCCCCCTGA  
GGCCAGTTCTGTATGGATGCTGTCTTGAGAATAACTTGCTGTCCCGGTGTCACCTGCTT  
CCATCTCCAGCCACCAGCCCTCTGCCACCTCACATGCCTCCCCATGGATTGGGGCCT  
CCCAGGCCCCCACCTTATGTCAACCTGCATTCTTGTTCAAAAATCAGGAAAAGAAAAG  
ATTTGAAGACCCCAAGTCTTGTCAATAACTTGCTGTGTGGAAGCAGCGGGGGAAGACCTA  
GAACCTTTTCCCAGCACTTGTTTTTCCAACATGATATTTATGAGTAATTTATTTTGATA  
TGTACATCTCTATTTTCTTACATTATTTATGCCCCCAAATTATATTTATGTATGTAAGT  
GAGGTTTGTTTTGTATATTAAAATGGAGTTTGTTTGT



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**FIGURE 78**

MRSGCVVHVWILAGLWLAVAGRPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFL  
RIRADGVVDCARGQSAHSLLEIKAVLRRTVAIKGVHVRVRYLCMGADGKMQGLLQYSEEDC  
AFEEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLR  
GHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSF EK

**Signal peptide:**  
amino acids 1-22

**Casein kinase II phosphorylation site:**  
amino acids 78-82, 116-120, 190-194, 204-208

**N-myristoylation site:**  
amino acids 15-21, 54-60, 66-72, 201-207

**Prokaryotic membrane lipoprotein lipid attachment site:**  
amino acids 48-59

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**FIGURE 79**

CGGACGCGTGGGCGGACGCGTGGGCCTGGGCAAGGGCCGGGGCGCCGGGCGGAGCCACCTCTTCCC  
CTCCCCCGCTTCCCTGTCGCGCTCCGCTGGCTGGACGCGCTGGAGGAGTGGAGCAGCACCCGGCCG  
GCCCTGGGGGCTGACAGTCGGCAAAGTTTGGCCCCAAGAGGAAGTGGTCTCAAACCCCGGCAGGTG  
GCGACCAGGCCAGACCAGGGGCGCTCGCTGCCTGCGGGCGGGCTGTAGGCGAGGGCGCGCCCCAGT  
GCCGAGACCCGGGGCTTCAGGAGCCGGCCCCCGGGAGAGAAGAGTGC GGCGGGCAGGAGAAAACA  
ACTCCAAAGTTGGCGAAAGGCACCGCCCCCTACTCCCGGGCTGCCGCGCCTCCCCGCCCCAGCCC  
TGGCATCCAGAGTACGGGTGAGCCCCGGGCCATGGAGCCCCCTGGGGAGGCGGCACACAGGGAGCC  
TGGGCGCCCCGGGGCTCCGCCGCGACCCCATCGGGTAGACACAGAAGCTCCGGGACCTTCCGGCA  
CCTCTGGACAGCCAGGATGCTGTTGGCCACCCTCCTCCTCCTCCTTGGAGGCGCTCTGGCCC  
ATCCAGACCGGATTATTTTCCAAATCATGCTTGTGAGGACCCCCCAGCAGTGCTCTTAGAAGTGC  
AGGGCACCTTACAGAGGCCCTGGTCCGGGACAGCCGCACCTCCCCTGCCAACTGCACCTGGCTCA  
TCCTGGGCAGCAAGGAACAGACTGTACCATCAGGTTCCAGAAGCTACACCTGGCCTGTGGCTCAG  
AGCGCTTAACCCCTACGCTCCCCTCTCCAGCCACTGATCTCCTGTGTGAGGCACCTCCAGCCCTC  
TGCAGCTGCCCGGGGGCAACGTACCATCACTTACAGCTATGCTGGGGCCAGAGCACCCATGGGCC  
AGGGCTTCTGCTCTCCTACAGCCAAGATTGGCTGATGTGCCTGCAGGAAGAGTTTCAGTGCCTGA  
ACCACCGCTGTGTATCTGCTGTCCAGCGCTGTGATGGGGTTGATGCCCTGTGGCGATGGCTCTGATG  
AAGCAGGTTGCAGCTCAGACCCCTTCCCTGGCCTGACCCCAAGACCCGTCCCCTCCCTGCCTTGCA  
ATGTCACCTTGGAGGACTTCTATGGGGTCTTCTCCTCTCCTGGATATACACACCTAGCCTCAGTCT  
CCCACCCCCAGTCTTGCCATTGGCTGCTGGACCCCCATGATGGCCGGCGGCTGGCCGTGCGCTTCA  
CAGCCCTGGACTTGGGCTTTGGAGATGCAGTGCACTGTGTATGACGGCCCTGGGCCCCCTGAGAGCT  
CCCGACTACTGCGTAGTCTCACCCACTTCAGCAATGGCAAGGCTGTCACTGTGGAGACACTGTCTG  
GCCAGGCTGTTGTGTCTTACCACACAGTTGCTTGGAGCAATGGTCGTGGCTTCAATGCCACCTACC  
ATGTGCGGGGCTATTGCTTGCCTTGGGACAGACCCCTGTGGCTTAGGCTCTGGCCTGGGAGCTGGCG  
AAGGCCTAGGTGAGCGCTGCTACAGTGAGGCACAGCGCTGTGACGGCTCATGGGACTGTGCTGACG  
GCACAGATGAGGAGGACTGCCCAGGCTGCCACCTGGACACTTCCCCTGTGGGGCTGCTGGCACCT  
CTGGTGCCACAGCCTGCTACCTGCCTGCTGACCGCTGCAACTACCAGACTTTCTGTGCTGATGGAG  
CAGATGAGAGACGCTGTGCGCATTGCCAGCCTGGCAATTTCCGATGCCGGGACGAGAAGTGCGTGT  
ATGAGACGTGGGTGTGCGATGGGCAGCCAGACTGTGCGGACGGCAGTGATGAGTGGGACTGCTCCT  
ATGTTCTGCCCCGCAAGGTCATTACAGCTGCAGTCAATTGGCAGCCTAGTGTGCGGCCTGCTCCTGG  
TCATCGCCCTGGGCTGCACCTGCAAGCTCTATGCCATTGCAACCCAGGAGTACAGCATCTTTGCCC  
CCCTCTCCCGGATGGAGGCTGAGATTGTGACAGCAGGACCCCCCTTCTACGGGCAGCTCATTG  
CCCAGGCTGCCATCCACCTGTAGAAGACTTCTTACAGAGAATCCTAATGATAACTCAGTGCTGG  
GCAACCTGCGTTCTCTGCTACAGATCTTACGCCAGGATATGACTCCAGGAGGTGGCCAGGTGCC  
GCCGTGCTCAGCGGGGCCGCTTGATGCGACGCTGGTACGCCGTCTCCGCCGCTGGGGCTTGCTCC  
CTCGAACCAACACCCCGGCTCGGGCCTCTGAGGCCAGATCCCAGGTCACACCTTCTGCTGCTCCCC  
TTGAGGCCCTAGATGGTGGCACAGGTCCAGCCCGTGAGGGCGGGGCGAGTGGGTGGGCAAGATGGGG  
AGCAGGCACCCCCACTGCCCATCAAGGCTCCCCCTCCCATCTGCTAGCACGTCTCCAGCCCCCACTA  
CTGTCCCTGAAGCCCCAGGGCCACTGCCCTCACTGCCCTTAGAGCCATCACTATTGTCTGGAGTGG  
TGCAGGCCCTGCGAGGCCGCTGTGCCCAGCCTGGGGCCCCCAGGACCAACCCGGAGCCCCCTG  
GACCCACACAGCAGTCTTGCCCTGGAAGATGAGGACGATGTGCTACTGGTGCCACTGGCTGAGC  
CGGGGTGTGGGTAGCTGAGGCAGAGGATGAGCCACTGCTTACCTGAGGGGACCTGGGGGCTCTAC  
TGAGGCCCTCTCCCCTGGGGGCTCTACTCATAGTGGCACAACTTTTAGAGGTGGGTGAGCCTCCCC  
TCCACCACTTCCCTTCCCTGTCCCTGGATTTAGGGACTTGGTGGGCCTCCCGTTGACCCATATGTAG  
CTGCTATAAAGTTAAGTGTCCCTCAGGCAGGGAGAGGCTCACAGAGTCTCCTCTGTACGTGGCCA  
TGGCCAGACACCCAGTCCCTTACCACCATCTGCTCCCAAGCCACCACCTTTGGGTGGCTGTT  
TTTAAAGTAAGTTCTTAGAGGATCATAGGTCTGGACACTCCATCCTTGCCAAACCTCTATCCCA  
AAAGTGGCCTTAAGCACCGGAATGCCAATTAAGTAGAGACCTCCAGCCCCCAAGGGGAGGATTTG  
GGCAGAACCTGAGGTTTGGCCATCCACAATCCCTCCTACAGGGCCTGGCTCACAAAAGAGTGCAA  
CAATGCTTCTATTCCATAGCTACGGCATTGCTCAGTAAGTTGAGGTCAAAAATAAGGAATCATA  
CATCTC

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**FIGURE 80**

MLLATLLLLLLGGALAHPDRIIFPNHACEDPPAVLLEVQGTLQRPLVRDSRTSPANCTWL  
ILGSKEQTVTIRFQKLHLACGSERLTLRSPLQPLISLCEAPPSPLQLPGGNVTITYSYAG  
ARAPMGQGFLSYSQDWLMCLQEEFQCLNHRCVSAVQRCDGVDACGDGSDEAGCSSDPFF  
GLTPRPVPSLPCNVLTLEDYGVFSSPGYTHLASVSHQPQCHWLLDPHDGRRRLAVRFTALD  
LGFGDAVHVYDGPPESSRLRLSLTHFSNGKAVTVETLSGQAVVSYHTVAWSNGRGFNA  
TYHVRGYCLPWDRPCGLGSGLGAGEGLGERCYSEAQRCDGSWDCADGTDEEDCPGCPPGH  
FPCGAAGTSGATACYPADRCNYQTFCADGADERRCRHCQPGNFRRCRDEKCVYETWVCDG  
QPD CADGSDEWDCSYVLPRKVITA AVIGSLVCGLLLVIALGCTCKLYAIRTQEYSIFAPL  
SRMEAEIVQQQAPPSYGQLIAQGAIPPVEDFPTENPNDNSVLGNLRSLLQILRQDMTPGG  
GPGARRRQRGRMLMRRLLVRRRLRWGLLPRTNTPARASEARSQVTPSAAPLEALDGGTGPAR  
EGGAVGGQDGEQAPPLPIKAPLPSASTSPAPTTVPEAPGPLPSLPLEPSLLSGVVQALRG  
RLLP SLGPPGPTRSPPGPHTAVLALEDEDDVLLVPLAEPGVWVAEAEDEPLLT

**Important features:****Signal peptide:**

amino acids 1-16

**Transmembrane domain:**

amino acids 442-462

**LDL-receptor class A (LDLRA) domain proteins:**

amino acids 411-431, 152-171, 331-350 and 374-393

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**FIGURE 81**

CTTCTGTGCTGTTCTTCTTGCCTCTAACTTGTAACAAGACGTACTAGGACGATGCTAA  
TGGAAAGTCACAAACCGCTGGGTTTTTGAAGGATCCTTGGGACCTCATGCACATTTGTG  
GAAACTGGATGGAGAGATTTGGGGAAGCATGGACTCTTTAGCCAGCTTAGTTCTCTGTGG  
AGTCAGCTTGCTCCTTTCTGGAAGTGTGGAAGGTGCCATGGACTTGATCTTGATCAATTC  
CCTACCTCTTGTATCTGATGCTGAAACATCTCTCACCTGCATTGCCTCTGGGTGGCGCCC  
CCATGAGCCCATCACCATAGGAAGGGACTTTGAAGCCTTAATGAACCAGCACCAGGATCC  
GCTGGAAGTTACTCAAGATGTGACCAGAGAATGGGCTAAAAAAGTTGTTTGGAAGAGAGA  
AAAGGCTAGTAAGATCAATGGTGCTTATTTCTGTGAAGGGCGAGTTCGAGGAGAGGCAAT  
CAGGATACGAACCATGAAGATGCGTCAACAAGCTTCCTTCTACCAGCTACTTTAACTAT  
GACTGTGGACAAGGGAGATAACGTGAACATATCTTTCAAAAAGGTATTGATTAAAGAAGA  
AGATGCAGTGATTTACAAAAATGGTTCCTTCATCCATTCAGTGCCCCGGCATGAAGTACC  
TGATATTCTAGAAGTACACCTGCCTCATGCTCAGCCCCAGGATGCTGGAGTGTACTCGGC  
CAGGTATATAGGAGGAAACCTCTTCACCTCGGCCTTCACCAGGCTGATAGTCCGGAGATG  
TGAAGCCCAGAAGTGGGGACCTGAATGCAACCATCTCTGTACTGCTTGTATGAACAATGG  
TGTCTGCCATGAAGATACTGGAGAATGCATTTGCCCTCCTGGGTTTATGGGAAGGACGTG  
TGAGAAGGCTTGTGAAGTGCACACGTTTGGCAGAACTTGTAAGAAAGGTGCAGTGGACA  
AGAGGGATGCAAGTCTTATGTGTTCTGTCTCCCTGACCCCTATGGGTGTTCTGTGCCAC  
AGGCTGGAAGGGTCTGCAGTGCAATGAAGCATGCCACCCTGGTTTTTACGGGCCAGATTG  
TAAGCTTAGGTGCAGCTGCAACAATGGGGAGATGTGTGATCGCTTCCAAGGATGTCTCTG  
CTCTCCAGGATGGCAGGGGCTCCAGTGTGAGAGAGAAGGCATACCGAGGATGACCCCAA  
GATAGTGGATTTGCCAGATCATATAGAAGTAAACAGTGGTAAATTTAATCCCATTTGCAA  
AGCTTCTGGCTGGCCGCTACCTACTAATGAAGAAATGACCCTGGTGAAGCCGGATGGGAC  
AGTGCTCCATCCAAAAGACTTTAACCATACGGATCATTTCTCAGTAGCCATATTCACCAT  
CCACCGGATCCTCCCCCTGACTCAGGAGTTTGGGTCTGCAGTGTGAACACAGTGGCTGG  
GATGGTGGAAAAGCCCTTCAACATTTCTGTAAAGTTCTTCCAAAGCCCCCTGAATGCCCC  
AAACGTGATTGACACTGGACATAACTTTGCTGTCATCAACATCAGCTCTGAGCCTTACTT  
TGGGGATGGACCAATCAAATCCAAGAAGCTTCTATACAAACCCGTTAATCACTATGAGGC  
TTGGCAACATATTCAGTGACAAATGAGATTGTTACACTCAACTATTTGGAACCTCGGAC  
AGAATATGAACTCTGTGTGCAACTGGTCCGTCGTGGAGAGGGTGGGGAAGGGCATCCTGG  
ACCTGTGAGACGCTTCACAACAGCTTCTATCGGACTCCCTCCTCCAAGAGGTCTAAATCT  
CCTGCCTAAAAGTCAGACCACTCTAAATTTGACCTGGCAACCAATATTTCCAAGCTCGGA  
AGATGACTTTTATGTTGAAGTGGAGAGAAGGTCTGTGCAAAAAGTGATCAGCAGAATAT  
TAAAGTTCAGGCAACTTGACTTCGGTGCTACTTAACAACCTTACATCCCAGGGAGCAGTA  
CGTGGTCCGAGCTAGAGTCAACACCAAGGCCAGGGGAATGGAGTGAAGATCTCACTGC  
TTGGACCCTTAGTGACATTCTTCCTCCTCAACCAGAAAACATCAAGATTTCCAACATTAC  
ACACTCCTCGGCTGTGATTTCTTGACAATATTGGATGGCTATTCTATTTCTTCTATTAC  
TATCCGTTACAAGGTTCAAGGCAAGAATGAAGACCAGCACGTTGATGTGAAGATAAAGAA  
TGCCACCATCATTCAAGTATCAGCTCAAGGGCCTAGAGCCTGAAACAGCATACCAGGTGGA  
CATTTTTGTCAGAGAACAACATAGGGTCAAGCAACCCAGCCTTTTCTCATGAACTGGTGAC  
CCTCCCAGAATCTCAAGCACCAGCGGACCTCGGAGGGGGGAAGATGCTGCTTATAGCCAT  
CCTTGGCTCTGCTGGAATGACCTGCCTGACTGTGCTGTTGGCCTTTCTGATCATATTGCA  
ATTGAAGAGGGCAAATGTGCAAAGGAGAATGGCCCAAGCCTTCCAAAACGTGAGGGGAAGA  
ACCAGCTGTGCAGTTCAACTCAGGGACTCTGGCCCTAAACAGGAAGGTCAAAAACAACCC  
AGATCCTACAATTTATCCAGTGCTTGACTGGAATGACATCAAATTTCAAGATGTGATTGG  
GGAGGGCAATTTTGGCCAAGTTCTTAAGGCGCGCATCAAGAAGGATGGGTTACGGATGGA  
TGCTGCCATCAAAAGAATGAAAGAATATGCCTCAAAGATGATCACAGGGACTTTGCAGG  
AGAAGTGAAGTTCTTTGTAAACTTGACACCATCCAAACATCATCAATCTCTTAGGAGC

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ATGTGAACATCGAGGCTACTTGTACCTGGCCATTGAGTACGCGCCCCATGGAAACCTTCT  
GGACTTCCTTCGCAAGAGCCGTGTGCTGGAGACGGACCCAGCATTTGCCATTGCCAATAG  
CACCGCGTCCACACTGTCTCCAGCAGCTCCTTCACTTCGCTGCCGACGTGGCCCGGGG  
CATGGACTACTTGAGCCAAAAACAGTTTATCCACAGGGATCTGGCTGCCAGAAACATTTT  
AGTTGGTGAAAACTATGTGGCAAAAATAGCAGATTTTGGATTGTCCCGAGGTCAAGAGGT  
GTACGTGAAAAAGACAATGGGAAGGCTCCAGTGCGCTGGATGGCCATCGAGTCACTGAA  
TTACAGTGTGTACACAACCAACAGTGATGTATGGTCCTATGGTGTGTTACTATGGGAGAT  
TGTTAGCTTAGGAGGCACACCCTACTGCGGGATGACTTGTGCAGAACTCTACGAGAAGCT  
GCCCCAGGGCTACAGACTGGAGAAGCCCCCTGAAGTGTGATGATGAGGTGTATGATCTAAT  
GAGACAATGCTGGCGGGAGAAGCCTTATGAGAGGCCATCATTTGCCCAGATATTGGTGTC  
CTTAAACAGAATGTTAGAGGAGCGAAAGACCTACGTGAATACCACGCTTTATGAGAAGTT  
TACTTATGCAGGAATTGACTGTTCTGCTGAAGAAGCGGCCTAGGACAGAACATCTGTATA  
CCCTCTGTTTTCCCTTTCACTGGCATGGGAGACCCTTGACAACTGCTGAGAAAACATGCCT  
CTGCCAAAGGATGTGATATATAAGTGTACATATGTGCTGGAATTCTAACAAGTCATAGGT  
TAATATTTAAGACACTGAAAAATCTAAGTGATATAAATCAGATTCTTCTCTCTCATTTTA  
TCCCTCACCTGTAGCATGCCAGTCCCGTTTCATTTAGTCATGTGACCACTCTGTCTTG TG  
TTTCCACAGCCTGCAAGTTCAGTCCAGGATGCTAACATCTAAAAATAGACTTAAATCTCA  
TTGCTTACAAGCCTAAGAATCTTTAGAGAAGTATACATAAGTTTAGGATAAAATAATGGG  
ATTTTCTTTTCTTTTCTCTGGTAATATTGACTTGTATATTTTAAGAAATAACAGAAAGCC  
TGGGTGACATTTGGGAGACATGTGACATTTATATATTGAATTAATATCCCTACATGTATT  
GCACATTGTAAAAAGTTTTAGTTTTGATGAGTTGTGAGTTTACCTTGTATACTGTAGGCA  
CACTTTGCACTGATATATCATGAGTGAATAAATGTCTTGCCCTACTCAAAAAAAAAA

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**FIGURE 82**

MDSLASLVLCGVSLLLSGTVEGAMDLILINSLPLVSDAETSLTCIASGWRPHEPITIGRD  
FEALMNQHQDPLEVTQDVTREWAKKVWVKREKASKINGAYFCEGRVVRGEAIRIRTMKMRQ  
QASFLPATLTMTVDKGDVNISFKKVLKEEDAVIYKNGSFIHSVPRHEVPDILEVHLPH  
AQPQDAGVYSARYIGGNLFTSAFTRLIVRRCEAQKWGPECNHLCTACMNGVCHEDTGEC  
ICPPGFMGRTCEKACELHTFGRTCKERCSCGQEGCKSYVFCLPDYPYGCSCATGWKGLQCNE  
ACHPGFYGPDCKLRCSNNGEMCDRFQGCCLSPGWQGLQCEREGIPRMTPKIVDLPDHIE  
VNSGKFNPICKASGWPLPTNEEMTLVKPDGTVLHPKDFNHTDHFSAIFTIHRILPPDSG  
VWVCSVNTVAGMVEKPFNISVKVLPKPLNAPNVIDTGHNFAVINISSEPYFGDGPIKSKK  
LLYKPVNHYEAWQHIQVTNEIVTLNYLEPRTEYELCVQLVRRGEGGEGHPGPVRRFTTAS  
IGLPPPRGLNLLPKSQTTLNLTWQPIFPSEDDFYVEVERRSVQKSDQQNIKVPGNLTSV  
LLNNLHPREQYVVRARVNTKAQGEWSEDLTAWTLSDILPPQPENIKISNITHSSAVISWT  
ILDGYSISSITIRYKVQGNEDQHVDVKIKNATIIQYQLKGLEPETAYQVDIFAENNIGS  
SNPAFSHELVTLPESQAPADLGGGKMLLIAILGSAGMTCLTVLLAFLIILQLKRANVQRR  
MAQAFQNVREEPAVQFNSGTLALNRKVKNPDPTIYPVLDWNDIKFQDVI GEGNFGQVLK  
ARIKKDGLRMDAAIKRMKEYASKDDHRDFAGELEVLCKLGHPNIIINLLGACEHRGYLYL  
AIEYAPHGNLLDFLRKSRVLETDPAFAIANSTASTLSSQQLLHFAADVARGMDYLSQKQF  
IHRDLAARNILVGENYVAKIADFGLSRGQEVYVKKTMGRLPVRWMAIESLNYSVYTTNSD  
VWSYGVLLWEIVSLGGTPYCGMTCAELYEKLPGYRLEKPLNCDDEVYDLMRQCWREKPY  
ERPSFAQILVSLNRMLEERKTYVNTTLYEKFTYAGIDCSAEAEA

**Signal sequence:**

1-38

**Transmembrane domain:**

750-770

**N-glycosylation site:**

140-143, 158-161, 399-402, 438-441, 464-467, 560-563, 596-599, 649-652, 691-694, 930-933, 1011-1014, 1104-1107

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

534-537

**Tyrosine kinase phosphorylation site:**

149-156, 808-816, 1094-1102

**N-myristoylation site:**

18-23, 98-103, 187-192, 196-201, 270-275, 286-291, 295-300, 420-425, 595-600, 984-989, 1036-1041, 1041-1046, 1115-1120

**Prokaryotic membrane lipoprotein lipid attachment site:**

882-892

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**EGF-like domain cysteine pattern signature:**

240-251, 287-298, 329-340

**Tyrosine protein kinases specific active-site signature:**

960-972

**Protein kinase domain:**

824-1092

**Fibronectin type III domain:**

444-529, 543-626, 639-724

**EGF-like domain:**

220-251, 268-298

**laminin\_EGF Laminin EGF-like (Domains III and V):**

219-268

**Immunoglobulin domain:**

156-193

**Zinc finger:**

295-313

**Receptor tyrosine kinase:**

844-868, 869-898, 936-982, 986-1024, 1025-1052, 1052-1088

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**FIGURE 83**

CGCGCCGGGCGCAGGGAGCTGAGTGGACGGCTCGAGACGGCGGCGCGTGCAGCAGCTCCA  
GAAAGCAGCGAGTTGGCAGAGCAGGGCTGCATTTCCAGCAGGAGCTGCGAGCACAGTGCT  
GGCTCACAACAAGATGCTCAAGGTGTCAGCCGTACTGTGTGTGTGTGCAGCCGCTTGGTG  
CAGTCAGTCTCTCGCAGCTGCCGCGGCGGTGGCTGCAGCCGGGGGGCGGTCCGACGGCGG  
TAATTTTCTGGATGATAAACAATGGCTCACCACAATCTCTCAGTATGACAAGGAAGTCCG  
ACAGTGGAACAAATTCGAGACGAAGTAGAGGATGATTATTTCCGCACTTGGAGTCCAGG  
AAAACCCCTTCGATCAGGCTTTAGATCCAGCTAAGGATCCATGCTTAAAGATGAAATGTAG  
TCGCCATAAAGTATGCATTGCTCAAGATTCTCAGACTGCAGTCTGCATTAGTCACCGGAG  
GCTTACACACAGGATGAAAGAAGCAGGAGTAGACCATAGGCAGTGGAGGGGTCCCATATT  
ATCCACCTGCAAGCAGTGCCAGTGCTCTATCCCAGCCCTGTTTGTGGTTTCAGATGGTCA  
TACCTACTCTTTTCAGTGCAAATAAGATATCAGGCATGTGTCTTAGGAAAACAGATCTC  
AGTCAAATGTGAAGGACATTGCCCATGTCTTCAGATAAGCCCACCAGTACAAGCAGAAA  
TGTTAAGAGAGCATGCAGTGACCTGGAGTTCAGGGAAGTGGCAAACAGATTGCGGGACTG  
GTTCAAGGCCCTTCATGAAAGTGGAAGTCAAAACAAGAAGACAAAAACATTGCTGAGGCC  
TGAGAGAAGCAGATTGATACAGCATCTTGCCAATTTGCAAGGACTCACTTGGCTGGAT  
GTTTAAACAGACTTGATACAACTATGACCTGCTATTGGACCAGTCAGAGCTCAGAAGCAT  
TTACCTTGATAAGAATGAACAGTGTACCAAGGCATTCTTCAATTCTTGTGACACATACAA  
GGACAGTTTAAATATCTAATAATGAGTGGTGCTACTGCTTCCAGAGACAGCAAGACCCACC  
TTGCCAGACTGAGCTCAGCAATATTCAGAAGCGGCAAGGGGTAAAGAAGCTCCTAGGACA  
GTATATCCCCCTGTGTGATGAAGATGGTTACTACAAGCCAACACAATGTCATGGCAGTGT  
TGGACAGTGCTGGTGTGTTGACAGATATGGAAATGAAGTCATGGGATCCAGAATAAATGG  
TGTTGCAGATTGTGCTATAGATTTTGAGATCTCCGGAGATTTTGCTAGTGGCGATTTTCA  
TGAATGGACTGATGATGAGGATGATGAAGACGATATTATGAATGATGAAGATGAAATTGA  
AGATGATGATGAAGATGAAGGGGATGATGATGATGGTGGTGGTATGACCATGATGTATACAT  
TTGATTGATGACAGTTGAAATCAATAAATTCTACATTTCTAATATTTACAAAAATGATAG  
CCTATTTTAAATTTATCTTCTTCCCCAATAACAAAATGATTCTAAACCTCACATATATTTT  
GTATAATTATTTGAAAAATTCAGCTAAAGTTATAGAAGTTTATGTTTAAATAAGAATCA  
TTTGCTTTGAGTTTTTATATTCCTTACACAAAAGAAAATACATATGCAGTCTAGTCAGA  
CAAAATAAAGTTTTGAAGTGCTACTATAATAAATTTTTCACGAGAACAACTTTGTAAAT  
CTTCATAAGCAAAATGACAGCTAGTGCTTGGGATCGTACATGTTAATTTTTTGAAAGAT  
AATTCTAAGTGAAATTTAAATAAATAAATTTTAAATGACCTGGGTCTTAAGGATTTAGG  
AAAAATATGCATGCTTTAATTGCATTTCCAAAGTAGCATCTTGCTAGACCTAGATGAGTC  
AGGATAACAGAGAGATACCACATGACTCCAAAAAAAAAAAAAAAAA



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**FIGURE 84**

MLKVSAVLCVCAAAWCSQSLAAAAVAAGGRSDGGNFLDDKQWLTTISQYDKEVGQWNK  
FRDEVEDDYFRTWSPGKPFQALDPAKDPCLKMKCSRHKVCIAQDSQTAVCISHRRLTHR  
MKEAGVDHRQWRGPILSTCKQCPVVYPSPVCGSDGHTYSFQCKLEYQACVLGKQISVKCE  
GHCPSPDKPTSTSRNVKRACSDLEFREVANRLRDWFKALHESGSQNKKTLLRPERSR  
FDTSILPICKDSLGMFMNRLDTNYDLLDQSELRSIYLDKNEQCTKAFFNSCDTYKDSL  
SNNEWCYCFQRQQDPPCQTELSNIQKRQGVKKLLGQYIPLCDEDGYKPTQCHGSVGQCW  
CVDRYGNEVMGSRINGVADCAIDFEISGDFASGDFHEWTDDEDDDDIMNDEDEIEDDDE  
DEGDDDDGGDDHDVYI

**Important features:**

**Signal peptide:**

amino acids 1-16

**Leucine zipper pattern:**

amino acids 246-267

**N-myristoylation sites:**

amino acids 357-362, 371-376 and 376-381

**Thyroglobulin type-1 repeat proteins:**

amino acids 353-365 and 339-352

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**FIGURE 85**

CCCACGCGTCCGGCACTGCAGTCTCCAGCCTGAGCCATGGGCCGCGGAGCCCTCCTGCTC  
CTGCTTCTGTCTTTTCTGGCGCCCTGGGCCACCATAGCCCTCCGGCCGGCCTTAAGGGCC  
CTCGGCAGCCTACACTTGCCAACCAACCCACATCCCTCCCGGCTGTAGCCAAGAACTAT  
TCGGTTCTCTACTTCCAACAGAAGGTTGATCATTTTGGATTTAATACTGTGAAAACTTTT  
AATCAGCGGTACCTAGTAGCTGATAAATACTGGAAGAAAAATGGTGGATCAATACTTTTC  
TACACTGGTAATGAAGGGGACATTATCTGGTTTTGTAAATAACACGGGGTTTCATGTGGGAT  
GTGGCTGAGGAAGTGAAGCTATGTTGGTGTGTTGCTGAACATCGATACTATGGAGAGTCT  
CTCCCCCTTTGGTGACAACTCATTCAAGGATTCCAGACACTTGAATTTCTTGACATCAGAA  
CAAGCTCTGGCTGATTTTGCAGAGTTAATCAAACACTTGAAAAGAACAATCCCAGGAGCT  
GAAAATCAACCTGTTCATTGCCATAGGAGGCTCCTATGGTGGCATGCTTGCCGCCTGGTTTT  
AGGATGAAATATCCTCATATGGTAGTTGGAGCTCTTGACAGCTTCTGCCCTATCTGGCAG  
TTTGAGGATTTAGTACCTTGTGGTGTATTTATGAAGATCGTAACTACAGATTTTAGGAAA  
AGCGGTCCACATTGTTTCAGAGAGCATCCACAGGTCTGGGATGCCATTAATCGACTCTCA  
AATACTGGCAGTGGTTTGCAGTGGCTTACTGGAGCCCTTCACTTATGCAGCCCATTAACT  
TCTCAGGACATCCAACATTTGAAAGACTGGATCTCTGAAACCTGGGTGAATCTGGCAATG  
GTGGACTATCCTTATGCCTCTAACTTTTTACAGCCTTGCCTGCTTGGCCTATCAAGGTA  
GTGTGCCAGTATTTGAAAAATCCCAATGTATCTGATTCACTGCTGCTGCAGAATATTTTC  
CAAGCTCTGAATGTATATTACAATTATTCGGGCCAGGTGAAATGCCTGAATATTTTCAGAG  
ACAGCAACTAGCAGTCTGGGAACACTGGGTGGAGCTATCAGGCCTGCACAGAAGTAGTC  
ATGCCCTTTTGTACTAATGGTGTGATGACATGTTTGAACCTCACTCATGGAACCTTAAAG  
GAACTTTCTGATGACTGTTTTCAACAGTGGGGTGTGAGACCAAGGCCCTCCTGGATCACT  
ACTATGTATGGAGGCAAAAACATTAGTTTACACACAAAACATTGTTTTTCAGCAATGGTGAA  
CTAGACCCCTGGTCAGGAGGTGGAGTAACTAAGGATATCACAGACACTCTGGTTGCAGTC  
ACCATCTCAGAGGGGGCCCACTTAGATCTCCGCACCAAGAATGCCTTGGATCCTATG  
TCTGTGCTGTTAGCCCGCTCCTTGGAAGTTAGACATATGAAGAATTGGATCAGAGATTTTC  
TATGACAGTGCGGGAAAGCAGCACTGAGAACTTTTTGATTGTTTTCAATTTCTTCTTTTA  
TGTTTACACCACCACATTCCCATTCACCTTGATTTTCTACATGTAATTACCTTCTTTTGT  
TTATCATTAGATTTGATGGGGCCAAAGTTGAGATAGAATAGAGGGTGATGACGGTAAGAG  
CAAGTGTCCCATGAATGTGATTTCTGGGTCTCACTGTCTTTGCACCACGTCTAGGAA  
GAATCTTCTTGATAGCTCTCCACACCATCAGTGGCCCTCATAACTGGAGTAGAGTTCTCCT  
GGTTGCTTTTCATAAGAGGGAGAGTTACTTTC

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**FIGURE 86**

MGRRALLLLLLSFLAPWATIALRPALRALGSLHLPTNPTSLPAVAKNYSVLYFQQKVDHF  
GFNTVKTFFNQRYLVADKYWKKNGGSILFYTGNEGDIIWFCNNTGFMWDVAEELKAMLVFA  
EHRYYGESLPFGDNSFKDSRHLNFLTSEQALADFAELIKHLKRTIPGAENQPVIAIGGSY  
GGMLAAWFRMKYPHVVVGALAASAPIWQFEDLVPCGVFMKIVTTDFRKSGPHCSESIHRS  
WDAINRLSNTGSGLQWLTGALHLCSPLTSQDIQHLKDWISETWVNLAMVDYPYASNFLQP  
LPAWPIKVVCQYLKNPNVSDSLLLQNI FQALNVYYNYSGQVKCLNISETATSSLGTLGWS  
YQACTEVVMPFCTNGVDDMFEPHSWNLKELSDDCFQQWGVPRPSWITTMYGKKNISSHT  
NIVFSNGELDPWSGGGVTKDITDTLVAVTISEGAHHLDLRTKNALDPMSVLLARSLEVRH  
MKNWIRDFYDSAGKQH

**Signal sequence:**

1-18

**Transmembrane domain:**

None

**N-glycosylation site:**

47-50, 101-104, 317-320, 336-339, 345-348, 415-418

**Glycosaminoglycan attachment site:**

433-436

**N-myristoylation site:**

178-183, 181-186, 182-187, 198-203, 339-344, 434-439

**Amidation site:**

1-4

**alpha/beta hydrolase fold:**

115-372

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**FIGURE 87**

GGCGGCGTCCGTGAGGGGCTCCTTTGGGCAGGGGTAGTGTTTGGTGTCCTGTCTTGCGT  
GATATTGACAACTGAAGCTTTCCTGCACCACTGGACTTAAGGAAGAGTGTA CTCTCGTAGG  
CGGACAGCTTTAGTGGCCGGCCGGCCGCTCTCATCCCCGTAAGGAGCAGAGTCCTTTGT  
ACTGACCAAGATGAGCAACATCTACATCCAGGAGCCTCCACGAATGGGAAGGTTTTATT  
GAAAACTACAGCTGGAGATATTGACATAGAGTTGTGGTCCAAAGAAGCTCCTAAAGCTTG  
CAGAAATTTTATCCAACCTTTGTTTGGGAAGCTTATTATGACAATACCATTTTTCATAGAGT  
TGTGCCTGGTTTCATAGTCCAAGGCGGAGATCCTACTGGCACAGGGAGTGGTGGAGAGTC  
TATCTATGGAGCGCCATTCAAAGATGAATTTTCATTACCGTTGCGTTTTAATCGGAGAGG  
ACTGGTTGCCATGGCAAATGCTGGTTCTCATGATAATGGCAGCCAGTTTTTCTTCACACT  
GGGTGAGCAGATGAACTTAACAATAAGCATAACCATCTTTGGAAGGTTACAGGGGATAC  
AGTATATAACATGTTGCGACTGTCAGAAGTAGACATTGATGATGACGAAAGACCACATAA  
TCCACACAAAATAAAAAGCTGTGAGGTTTTGTTTAAATCCTTTTGATGACATCATTTCCAAG  
GGAAATTAAAAGGCTGAAAAAGAGAAACCAGAGGAGGAAGTAAAGAAATTGAAACCCAA  
AGGCACAAAAAATTTAGTTTACTTTTCA TTTGGAGAGGAAGCTGAGGAAGAAGAGGAGGA  
AGTAAATCGAGTTAGTCAGAGCATGAAGGGCAAAAGCAAAAGTAGTCATGACTTGCTTAA  
GGATGATCCACATCTCAGTTCTGTTCCAGTTGTAGAAAGTGAAAAAGGTGATGCACCAGA  
TTTAGTTGATGATGGAGAAGATGAAAGTGCAGAGCATGATGAATATATTGATGGTGATGA  
AAAGAACCTGATGAGAGAAAGAATTGCCAAAAAATTAAAAAAGGACACAAGTGCGAATGT  
TAAATCAGCTGGAGAAGGAGAAGTGGAGAAGAAATCAGTCAGCCGCAGTGAAGAGCTCAG  
AAAAGAAGCAAGACAATTAAAACGGGAACCTTAGCAGCAAAACAAAAAAGTAGAAAA  
TGCAGCAAAACAAGCAGAAAAAAGAAGTGAAGAGGAAGAAGCCCCTCCAGATGGTGCTGT  
TGCCGAATACAGAAGAGAAAAAGCAAAAGTATGAAGCTTTGAGGAAGCAACAGTCAAAGAA  
GGGAACCTTCCCGGGAAGATCAGACCCTTGCACTGCTGAACCAGTTTAAATCTAACTCAC  
TCAAGCAATTGCTGAAACACCTGAAAATGACATTCTTGAAACAGAAGTAGAAGATGATGA  
AGGATGGATGTCACATGTACTTTCAGTTTGGAGGATAAAAGCAGAAAAGTGAAAGATGCAAG  
CATGCAAGACTCAGATACATTTGAAATCTATGATCCTCGGAATCCAGTGAATAAAAGAAG  
GAGGGAAGAAAGCAAAAAGCTGATGAGAGAGAAAAAAGAAAGAAGATATAAATGAGAATAA  
TGATAACCAGAACTTGCTGGAAATGTGCCTACAATGGCCTTGTAACAGCCATTGTTCCCA  
ACAGCATCACTTAGGGGTGTGAAAAGAAGTATTTTTGAACCTGTTGTCTGGTTTTGAAAA  
ACAATTATCTTGTTTTGC AAATTGTGGAATGATGTAAGCAAATGCTTTTGGTTACTGGTA  
CATGTGTTTTTTCCTAGCTGACCTTTTATATTGCTAAATCTGAAATAAAATAACTTTCT  
TCCACAAAAA

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**FIGURE 88**

MSNIYIQEPPTNGKVLLKTTAGDIDIELWSKEAPKACRNFIQLCLEAYDNTIFHRVVPG  
FIVQGGDPTGTGSGGESIYGAPFKDEFHSRLRFNRRGLVAMANAGSHDNGSQFFFTLGRA  
DELNNKHTIFGKVTGDTVYNMLRLSEVDIDDDERPHNPHKIKSCEVLFPFDDIIPREIK  
RLKKEKPEEEVKKLKPKGTKNFSLLSFGEAEAEAEAEAEVNRVSQSMKGKSKSSHDLKDDP  
HLSSVPVVESEKGDAPDLVDDGEDESAEHDEYIDGDEKNLMRERIAKKLKKDTSANVKSA  
GEGEVEKKS VSRSEELRKEARQLKRELLAAKQKKVENAAKQAEKRSEEEEAPPDGAVAEY  
RREKQKYEALRKQQSKKGT SREDQTLALLNQFKSKLTQAIAETPENDIPETEVEDDEGWM  
SHVLQFEDKSRKVKDASMQSDTFEIIDPRNPVNKRREESKMLREKKERR

**Important features:****Signal peptide:**

amino acids 1-21

**N-glycosylation sites:**

amino acids 109-112 and 201-204

**Cyclophilin-type peptidyl-prolyl cis-trans isomerase****signature:**

amino acids 49-66

**Homologous region to Cyclophilin-type peptidyl-prolyl cis-trans isomerase:**

amino acids 96-140, 49-89 and 22-51

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**FIGURE 89**

CCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTCGCGCGCCACGATGCTGCAGGGCCCTGG  
CTCGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGGCTCTT  
CCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATCCCGGTCAA  
CCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCCAACCTGCTGGGCCA  
CGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTGGTCATGAAGCA  
GTGCCACCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCCGTCTGCCTCGATGA  
CCTAGACGAGACCATCCAGCCATGCCACTCGCTCTGCGTGCAGGTGAAGGACCGCTGCGC  
CCCGGTCATGTCCGCCTTCGGCTTCCCCTGGCCCCGACATGCTTGAGTGCGACCGTTTCCC  
CCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCACCTCCTGCCAGCCACCGA  
GGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAACGACATAAT  
GGAAACGCTTTGTAAAAATGATTTTGCCTGAAAATAAAAGTGAAGGAGATAACCTACAT  
CAACCGAGATACCAAAATCATCCTGGAGACCAAGAGCAAGACCATTTACAAGCTGAACGG  
TGTGTCCGAAAGGGACCTGAAGAAATCGGTGCTGTGGCTCAAAGACAGCTTGCAGTGCAC  
CTGTGAGGAGATGAACGACATCAACGCGCCCTATCTGGTCATGGGACAGAAACAGGGTGG  
GGAGCTGGTGATCACCTCGGTGAAGCGGTGGCAGAAGGGGCAGAGAGAGTTCAAGCGCAT  
CTCCCGCAGCATCCGCAAGCTGCAGTGCTAGTCCCGGCATCCTGATGGCTCCGACAGGCC  
TGCTCCAGAGCACGGCTGACCATTTCTGCTCCGGGATCTCAGCTCCCGTTCCCCAAGCAC  
ACTCCTAGCTGCTCCAGTCTCAGCCTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCAT  
CCCCAGCATTTCTGAGTTATAAGGCCACAGGAGTGGATAGCTGTTTTACCTAAAGGAA  
AAGCCCACCCGAATCTTGTAGAAATATTCAAATAATAAAATCATGAATATTTTAA

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**FIGURE 90**

MLQGPGSLLLLFLASHCCLGSARGLFLFGQPDFS YKRSNCKPIPVNLQLCHGIEYQNMRL  
PNLLGHETMKEVLEQAGAWIPLVMKQCHPDTKKFLCSLFAPVCLDDLDETIQPCHSLCVQ  
VKDRCAPVMSAFGFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEEAPKVCEACKNKND  
DDNDIMETLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLNGVSEKDLKKSVLWLK  
DSLQCTCEEMNDINAPYLVMGQKQGGEVLVTSVKRWQKGQREFKRISRSIRKLQC

**Important features:**

**Signal peptide:**

amino acids 1-20

**Cysteine rich domain, homologous to frizzled N terminus:**

amino acids 6-153

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**FIGURE 91**

[illegible]





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**FIGURE 92**

MT PQSLLQTTLFLLSLLFLVQGAHGRGHREDFRFCSQRNQTHRSSLHYKPTPDLRISIEN  
SEEALTVHAPFPAAHPASRSFPDPRGLYHFCLYWNRHAGRLHLLYGKRD FLLSDKASSLL  
CFQHQEESLAQGPPLLATSVTSWWSPQNISLPSAASF TFSFHSPHTAAHNASVDMCELK  
RDLQLLSQFLKHPQKASRRPSAAPASQQLQSLESKLT SVRFMGDMVSFEEDRINATVWKL  
QPTAGLQDLHIHSRQEEEQSEIMEYSVLLPRTL FQRTKGRSGEAEKRLLLVD FSSQALFQ  
DKNSSQVLGEKVLGIVVQNTKVANLTEPVVLT FQHQLQPKNVTLQCVFWVEDPTLSSPGH  
WSSAGCETVRRETQTSCFCNHLTYFAVLMVSSVEVD AVHKHYLSLLSYVGCVVVSALACL V  
TIAAYLCSRVP LPCR RKPRDYTIKVHMNLLLA VFLLDTSFLLSEPVALTGSEAGCRASAI  
FLHFSLLTCLSWMGLEGYNLYRLVVEVFGTYVPGYLLKLSAMGWGFPIFLVTLVALVDVD  
NYGPIILAVHRTPEGVIYPSMCWIRDSLVS YITNLGLFSLVFLFNMA MLATMVVQILRLR  
PHTQKWSHVL TLLGLSLVLGLPWALIFFS FASGTFQLVVL YLFSIITSFQGF LIFIWYWS  
MRLQARGGPSPLKSN SDSARLP ISSGSTSSSRI

**Important features:****Signal peptide:**

amino acids 1-25

**Putative transmembrane domains:**amino acids 382-398, 402-420, 445-468, 473-491, 519-537,  
568-590 and 634-657**Microbodies C-terminal targeting signal:**

amino acids 691-693

**cAMP- and cGMP-dependent protein kinase phosphorylation sites:**

amino acids 198-201 and 370-373

**N-glycosylation sites:**amino acids 39-42, 148-151, 171-174, 234-237, 303-306, 324-  
327 and 341-344**G-protein coupled receptors family 2 proteins:**

amino acids 475-504

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**FIGURE 93**

CCCACGCGTCCGAAGGCAGACAAAGGTTCAATTTGTAAAGAAGCTCCTTCCAGCACCTCCT  
CTCTTCTCCTTTTGCCCAAACCTCACCCAGTGAGTGTGAGCATTTAAGAAGCATCCTCTGC  
CAAGACCAAAAGGAAAGAAGAAAAAGGGCCAAAAGCCAAAATGAAACTGATGGTACTTGT  
TTTCACCATTGGGCTAACTTTGCTGCTAGGAGTTCAAGCCATGCCTGCAAATCGCCTCTC  
TTGCTACAGAAAGATACTAAAAGATCACAACCTGTCAACAACCTTCCGGAAGGAGTAGCTGA  
CCTGACACAGATTGATGTCAATGTCCAGGATCATTTCTGGGATGGGAAGGGATGTGAGAT  
GATCTGTTACTGCAACTTCAGCGAATTGCTCTGCTGCCCAAAGACGTTTTCTTTGGACC  
AAAGATCTCTTTTCGTGATTCTTGCAACAATCAATGAGAATCTTCATGTATTCTGGAGAA  
CACCATTCTGATTTCCACAAACTGCACTACATCAGTATAACTGCATTTCTAGTTTCTA  
TATAGTGCAATAGAGCATAGATTCTATAAATTCTTACTTGTCTAAGACAAGTAAATCTGT  
GTTAAACAAGTAGTAATAAAAGTTAATTCAATCTAAAAAAAAAAAAA

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## FIGURE 94

MKLMVLVFTIGLTLLLGVQAMPANRLSCYRKILKDHNCHNLPEGVADLTQIDVNVQDHFWDGKGCEMICYCNFSELLCCPKDVFFGPKISFVIPCNNQ

**Important features:**

**Signal peptide:**

amino acids 1-20

**N-glycosylation site:**

amino acids 72-76

**Tyrosine kinase phosphorylation site:**

amino acids 63-71

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**FIGURE 95**

GAATTCCGGGCCCCAGGATGCCAACTTTGAATAGGATGAAGACTACAACTTGTTCCCTTC  
TCATCTGCATCTCCCTGCTCCAGCTGATGGTCCCAGTGAATACTGATGAGACCATAGAGA  
TTATCGTGGAGAATAAGGTCAAGGAACCTTCTTGCCAATCCAGCTAACTATCCCTCCACTG  
TAACGAAGACTCTCTCTTGCACTAGTGTCAAGACTATGAACAGATGGGCCTCCTGCCCTG  
CTGGGATGACTGCTACTGGGTGTGCTTGTGGCTTTGCCTGTGGATCTTGGGAGATCCAGA  
GTGGAGATACTTGCAACTGCCTGTGCTTACTCGTTGACTGGACCACTGCCCCGCTGCTGCC  
AACTGTCCTAAGAATGAAGAGGTGGAGAACCAGCTTTGATATGATGAATCTAACAAAAA  
CTGCAGTCTCAATTTGGAAATCTGACTCATGTGCCTTTAAATGTGTTCATATTGCCCATTT  
TACCCTGCTTCTTGAAATGCTTCTTGAAAAATAAAGACAAATTTGCATGTG

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## FIGURE 96

MKTTTCSELLICISLLQLMVPVNTDETIEIIVENKVKELLANPANYPSTVTKTLSCTSVK  
TMNRWASCPAGMTATGCACGFACGSWEIQSGDTCNCLCLLDWTTARCCQLS

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**FIGURE 97**

GAGGCAGAAAGGCAGAAAGGAGAAAATTTCAGGATAACTCTCCTGAGGGGTGAGCCAAGCC  
CTGCCATGTAGTGCACGCAGGACATCAACAAACACAGATAACAGGAAATGATCCATTCCC  
TGTGGTCACTTATTCTAAAGGCCCAACCTTCAAAGTTCAAGTAGTGATATGGATGACTC  
CACAGAAAGGGAGCAGTCACGCCTTACTTCTTGCCTTAAGAAAAGAGAAGAAATGAAACT  
GAAGGAGTGTGTTTTCCATCCTCCCACGGAAGGAAAGCCCCCTCTGTCCGATCCTCCAAAGA  
CGGAAAGCTGCTGGCTGCAACCTTGCTGCTGGCACTGCTGTCTTGCTGCCTCACGGTGGT  
GTCTTTCTACCAGGTGGCCGCCCTGCAAGGGGACCTGGCCAGCCTCCGGGCAGAGCTGCA  
GGGCCACCACGCGGAGAAGCTGCCAGCAGGAGCAGGAGCCCCCAAGGCCGGCCTGGAGGA  
AGCTCCAGCTGTACCGCGGGACTGAAAATCTTTGAACCACCAGCTCCAGGAGAAGGCAA  
CTCCAGTCAGAACAGCAGAAATAAGCGTGCCGTTTCAGGGTCCAGAAGAAACAGTCACTCA  
AGACTGCTTGCAACTGATTGCAGACAGTGAAACACCAACTATACAAAAAGGATCTTACAC  
ATTTGTTCCATGGCTTCTCAGCTTTAAAAGGGGAAGTGCCCTAGAAGAAAAAGAGAATAA  
AATATTGGTCAAAGAACTGGTTACTTTTTTATATATGGTCAGGTTTTATATACTGATAA  
GACCTACGCCATGGGACATCTAATTCAGAGGAAGAAGGTCCATGTCTTTGGGGATGAATT  
GAGTCTGGTGACTTTGTTTCGATGTATTCAAATATGCCTGAAACACTACCCAATAATTC  
CTGCTATTCAGCTGGCATTGCAAACTGGAAGAAGGAGATGAACTCCAATTGCAATACC  
AAGAGAAAATGCACAAATATCACTGGATGGAGATGTCACATTTTTTGGTGCATTGAACT  
GCTGTGACCTACTTACACCATGTCTGTAGCTATTTTCCTCCCTTTCTCTGTACCTCTAAG  
AAGAAAGAATCTAACTGAAAATACCAAAAAAAAAAAAAAAAAA

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**FIGURE 98**

MDDSTEREQSRLTSCLKKREEMKLKECVSILPRKESPSVRSSKDGKLLAATLLLALLSCC  
LTVVSFYQVAALQGD LASLRAELQGHHA EKLPAGAGAPKAGLEEAPAVTAGLKIFEPPAP  
GEGNSSQNSRNKRAVQGPEETVTQDCLQLIADSETPTIQKGSYTFVPWLLSFKRGSAL EE  
KENKILVKETGYFFIYGQVLYTDKTYAMGH LIQRKKVHVFGDELSLVTLFRCIQNMPETL  
PNNSCYSAGIAKLEEGDELQLAIPRENAQISLDGDVTFFGALKLL

**Transmembrane domain:**  
amino acids 47-72

**N-glycosylation site:**  
amino acids 124-127, 242-245

**cAMP- and cGMP-dependent protein kinase phosphorylation  
site:**  
amino acids 33-36, 173-176

**N-myristoylation site:**  
amino acids 96-101

**TNF family proteins:**  
amino acids 172-206



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**FIGURE 99**

CCGAGGTGGCGATCGCTGAGAGGCAGGAGGGCCGAGGCGGGCCTGGGAGGCGGCCCGGAG  
GTGGGGCGCCGCTGGGGCCGGCCCGCACGGGCTTCATCTGAGGGCGCACGGCCCGCGACC  
GAGCGTGCGGACTGGCCTCCCAAGCGTGGGGCGACAAGCTGCCGGAGCTGCAATGGGCCG  
CGGCTGGGGATTCTTGTGTTGGCCTCCTGGGCGCCGTGTGGCTGCTCAGCTCGGGCCACGG  
AGAGGAGCAGCCCCCGGAGACAGCGGCACAGAGGTGCTTCTGCCAGGTTAGTGGTTACTT  
GGATGATTGTACCTGTGATGTTGAAACCATTGATAGATTTAATAACTACAGGCTTTTCCC  
AAGACTACAAAACTTCTTGAAAGTGACTACTTTAGGTATTACAAGGTAAACCTGAAGAG  
GCCGTGTCCTTTCTGGAATGACATCAGCCAGTGTGGAAGAAGGGACTGTGCTGTCAAACC  
ATGTCAATCTGATGAAGTTCCTGATGGAATTAAATCTGCGAGCTACAAGTATTCTGAAGA  
AGCCAATAATCTCATTGAAGAATGTGAACAAGCTGAACGACTTGGAGCAGTGGATGAATC  
TCTGAGTGAGGAAACACAGAAGGCTGTTCTTCAGTGGACCAAGCATGATGATTCTTCAGA  
TAACCTTCTGTGAAGCTGATGACATTGAGTCCCCTGAAGCTGAATATGTAGATTTGCTTCT  
TAATCCTGAGCGCTACACTGGTTACAAGGGACCAGATGCTTGGAAAATATGGAATGTCAT  
CTACGAAGAAAACGTGTTTTAAGCCACAGACAATTAAGAGACCTTTAAATCCTTTGGCTTC  
TGGTCAAGGGACAAGTGAAGAGAACACTTTTTACAGTTGGCTAGAAGGTCTCTGTGTAGA  
AAAAAGAGCATTCTACAGACTTATATCTGGCCTACATGCAAGCATTAATGTGCATTTGAG  
TGCAAGATATCTTTTACAAGAGACCTGGTTAGAAAAGAAATGGGGACACAACATTACAGA  
ATTTCAACAGCGATTTGATGGAATTTTGAAGTGAAGGAGAAGGTCCAAGAAGGCTTAAGAA  
CTTGTATTTTCTCTACTTAATAGAACTAAGGGCTTTATCCAAAGTGTTACCATTCTTCGA  
GCGCCAGATTTTCAACTCTTTACTGGAAATAAAATTCAGGATGAGGAAAACAAAATGTT  
ACTTCTGGAAATACTTCATGAAATCAAGTCATTTCTTTGCATTTTGATGAGAATTCATT  
TTTTGCTGGGGATAAAAAAGAAGCACACAACTAAAGGAGGACTTTCGACTGCATTTTAG  
AAATATTTCAAGAATTATGGATTGTGTTGGTTGTTTTAAATGTCGTCTGTGGGGAAAGCT  
TCAGACTCAGGGTTTGGGCACCTGCTCTGAAGATCTTATTTTCTGAGAAATTGATAGCAA  
TATGCCAGAAAGTGGACCTAGTTATGAATTCCATCTAACCAGACAAGAAATAGTATCATT  
ATTCAACGCATTTGGAAGAATTTCTACAAGTGTGAAAGAATTAGAAAACCTTCAGGAACTT  
GTTACAGAATATTCATTAAAGAAAAACAAGCTGATATGTGCCTGTTTCTGGACAATGGAGG  
CGAAAGAGTGGAATTTTCATTCAAAGGCATAATAGCAATGACAGTCTTAAGCCAAACATTT  
TATATAAAGTTGCTTTTGTAAAGGAGAATTATATTGTTTAAAGTAAACACATTTTAAAA  
ATTGTGTTAAGTCTATGTATAATACTACTGTGAGTAAAAGTAATACTTTAATAATGTGGT  
ACAAATTTTAAAGTTTAAATATTGAATAAAAGGAGGATTATCAAATTAATAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 100**

MGRGWGFLFGLLGAVWLLSSGHGEEQPPETAQAQRCFCQVSGYLDDCTCDVETIDRFNNYR  
LFPRLQKLLESDFRYKYNLKRPCPFWNDISQCGRRDCAVKPCQSDEVPDGIKSASYKY  
SEEANNLIEECEQAERLGAVDESLSEETQKAVLQWTKHDDSSDNFCEADDIQSPEAEYVD  
LLNPERYTGKGPDAWKIWNVIYEENCFKPQTIKRPLNPLASGQGTSEENTFYSWLEGL  
CVEKRAFYRLISGLHASINVHLSARYLLQETWLEKKWGHNITEFQQRFDGILTEGEGPRR  
LKNLYFLYLIELRALSKVLPFFERPDLFTGNKIQDEENKMLLLEILHEIKSFPLHFDE  
NSFFAGDKKEAHKLKEDFRLHFRNISRIMDCVGCFCRLWGKLQTQGLGTALKILFSEKL  
IANMPESGPSYEFHLTRQEIIVSLFNAFGRISTSVKELENFRNLLQNIH

**Important features:****Signal peptide:**

amino acids 1-23

**N-glycosylation site:**

amino acids 280-283 and 384-387

**Amidation site:**

amino acids 94-97

**Glycosaminoglycan attachment site:**

amino acids 20-23 and 223-226

**Aminotransferases class-V pyridoxal-phosphate:**

amino acids 216-222

**Interleukin-7 proteins:**

amino acids 338-343

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**FIGURE 101**

GCCTAGCCAGGCCAAGAATGCAATTGCCCCGGTGGTGGGAGCTGGGAGACCCCTGTGCTT  
GGACGGGACAGGGTCGGGGGACACGCAGGATGAGCCCCGCGACCACTGGCACATTCTTG  
TGACAGTGTACAGTATTTTCTCCAAGGTACACTCCGATCGGAATGTATACCCATCAGCAG  
GTGTCTCTTTGTTTCATGTTTTTGAAAGAGAATATTTTAAGGGGGAATTTCCACCTTACC  
CAAAACCTGGCGAGATTAGTAATGATCCCATAACATTTAATACAAATTTAATGGGTTACC  
CAGACCGACCTGGATGGCTTCGATATATCCAAAGGACACCATATAGTGATGGAGTCCTAT  
ATGGGTCCCCAACAGCTGAAAATGTGGGGAAGCCAACAATCATTGAGATAACTGCCTACA  
ACAGGCGCACCTTTGAGACTGCAAGGCATAATTTGATAATTAATATAATGTCTGCAGAAG  
ACTTCCCGTTGCCATATCAAGCAGAATTCCTTCATTAAGAATATGAATGTAGAAGAAATGT  
TGGCCAGTGAGGTTCTTGGGAGACTTTCTTGGCGCAGTGAAAAATGTGTGGCAGCCAGAGC  
GCCTGAACGCCATAAACATCACATCGGCCCTAGACAGGGGTGGCAGGGTGCCACTTCCCA  
TTAATGACCTGAAGGAGGGCGTTTATGTCATGGTTGGTGCAGATGTCCCGTTTTCTTCTT  
GTTTACGAGAAGTTGAAAATCCACAGAATCAATTGAGATGTAGTCAAGAAATGGAGCCTG  
TAATAACATGTGATAAAAAATTTTCGTACTCAATTTTACATTGACTGGTGCAAAATTTTCAT  
TGGTTGATAAAACAAAGCAAGTGTCCACCTATCAGGAAGTGATTCGTGGAGAGGGGATTT  
TACCTGATGGTGGAGAATACAAACCCCCCTTCTGATTCTTTGAAAAGCAGAGACTATTACA  
CGGATTTCTTAATTACACTGGCTGTGCCCTCGGCAGTGGCACTGGTCCTTTTTCTAATAC  
TTGCTTATATCATGTGCTGCCGACGGGAAGGCGTGGAAAAGAGAAACATGCAAAACACCAG  
ACATCCAACCTGGTCCATCACAGTGCTATTTCAGAAATCTACCAAGGAGCTTCGAGACATGT  
CCAAGAATAGAGAGATAGCATGGCCCCGTGCAACGCTTCCTGTGTTCCACCCTGTGACTG  
GGGAAATCATACTCCTTTACACACAGACAACTATGATAGCACAAACATGCCATTGATGC  
AAACGCAGCAGAACTTGCCACATCAGACTCAGATTCCCCAACAGCAGACTACAGGTAAAT  
GGTATCCCTGAAGAAAGAAAACCTGACTGAAGCAATGAATTTATAATCAGACAATATAGCA  
GTTACATCACATTTCTTTTCTTTCCAATAATGCATGAGCTTTTCTGGCATATGTTATGC  
ATGTTGGCAGTATTAAGTGTATACCAAATAATACAACTAATTTTCAATTTTACTAATGTA  
TTTTTTTGTACTTAAAGCATTTTTTGACAATTTGTAAAACATTGATGACTTTATATTTGTT  
ACAATAAAAGTTGATCTTTAAAATAAATATTATTAATGAAGCCTAAAAA

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**FIGURE 102**

MQLPRWWELGDPCAWTGQGRGTRRMSPATTGTFLTVYSIFSKVHSDRNVYPSAGVLFVH  
VLEREYFKGEFPPYPKPGEISNDPITFNTNLMGYPDRLPGWLRYIQRTPYSDGVLYGSPTA  
ENVGKPTIIETAYNRRTFETARHNLIIINIMSAEDFPLPYQAEFFIKNMNVEEMLASEVL  
GDFLGAVKNVWQPERLNAINITSALDRGGRVPLPINDLKEGVYVMVGADVFPSSCLREVE  
NPQNQLRCSQEMEPVITCDKKFRTQFYIDWCKISLVDKTKQVSTYQEVIRGEGILPDGGE  
YKPPSDSLKSRDYYTDFLITLAVPSAVALVFLILAYIMCCRREGVEKRNMQTPDIQLVH  
HSAIQKSTKELRDMSKNREIAWPLSTLPVFHPVTGEIIPPLHTDNYDSTNMPLMQTQQNL  
PHQTQIPQQOTTGKWYP

**signal sequence:**

Amino acids 1-46

**transmembrane domain:**

Amino acids 319-338

**N-glycosylation site:**

Amino acids 200-204

**cAMP- and cGMP-dependent protein kinase phosphorylation  
site:**

Amino acids 23-27

**Tyrosine kinase phosphorylation site:**

Amino acids 43-52

**N-myristoylation sites:**

Amino acids 17-23;112-118;116-122;185-191

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**FIGURE 103**

CAGAAGAGGGGGCTAGCTAGCTGTCTCTGCGGACCAGGGAGACCCCCGCGCCCCCGGT  
GTGAGGCGGCCTCACAGGGCCGGGTGGGCTGGCGAGCCGACGCGGCGGCGGAGGAGGCTG  
TGAGGAGTGTGTGGAACAGGACCCGGGACAGAGGAACCAATGGCTCCGCAGAACCTGAGCA  
CCTTTTGCCTGTTGCTGCTATACCTCATCGGGGCGGTGATTGCCGGACGAGATTTCTATA  
AGATCTTGGGGGTGCCTCGAAGTGCCTCTATAAAGGATATTAAAAAGGCCTATAGGAAAC  
TAGCCCTGCAGCTTCATCCCGACCGGAACCCCTGATGATCCACAAGCCCAGGAGAAATTCC  
AGGATCTGGGTGCTGCTTATGAGGTTCTGTGAGATAGTGAGAAACGGAAACAGTACGATA  
CTTATGGTGAAGAAGGATTAAAAGATGGTCATCAGAGCTCCCATGGAGACATTTTTTTCAC  
ACTTCTTTGGGGATTTTTGGTTTTCATGTTTTGGAGGAACCCCTCGTCAGCAAGACAGAAATA  
TTCCAAGAGGAAGTGATATTATTGTAGATCTAGAAGTCACTTTGGAAGAAGTATATGCAG  
GAAATTTTGTGGAAGTAGTTAGAAACAAACCTGTGGCAAGGCAGGCTCCTGGCAAACGGA  
AGTGCAATTGTGCGCAAGAGATGCGGACCACCCAGCTGGGGCCCTGGGCGCTTCCAAATGA  
CCCAGGAGGTGGTCTGCGACGAATGCCCTAATGTCAAACCTAGTGAATGAAGAACGAACGC  
TGGAAGTAGAAATAGAGCCTGGGGTGAGAGACGGCATGGAGTACCCCTTTATTGGAGAAG  
GTGAGCCTCACGTGGATGGGGAGCCTGGAGATTTACGGTTCCGAATCAAAGTTGTCAAGC  
ACCCAATATTTGAAAGGAGAGGAGATGATTTGTACACAAATGTGACAATCTCATTAGTTG  
AGTCACTGGTTGGCTTTGAGATGGATATTACTCACTTGGATGGTCACAAGGTACATATTT  
CCCGGGATAAGATCACCAGGCCAGGAGCGAAGCTATGGAAGAAAGGGGAAGGGCTCCCCA  
ACTTTGACAACAACAATATCAAGGGCTCTTTGATAATCACTTTTGATGTGGATTTTCCAA  
AAGAACAGTTAACAGAGGAAGCGAGAGAAGGTATCAAACAGCTACTGAAACAAGGGTCAG  
TGCAGAAGGTATACAATGGACTGCAAGGATATTGAGAGTGAATAAAAATTGGACTTTGTTT  
AAAATAAGTGAATAAGCGATATTTATTATCTGCAAGGTTTTTTTTTGTGTGTGTTTTTGT  
TTATTTTCAATATGCAGAGTTAGGCTTAATTTTTTTTATCTAATGATCATCATGAAATGAAT  
AAGAGGGCTTAAGAATTTGTCCATTTGCATTGCGAAAAGAAATGACCAGCAAAAGGTTTAC  
TAATACCTCTCCCTTTGGGGATTTAATGTCTGGTGCTGCCGCTGAGTTTCAAGAATTAA  
AGCTGCAAGAGGACTCCAGGAGCAAAAGAAACACAATATAGAGGGTTGGAGTTGTTAGCA  
ATTTCAATTCAAAATGCCAACTGGAGAAGTCTGTTTTTAAATACATTTTGTGTATTATTTTA

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**FIGURE 104**

MAPQNLSTFCLLLLYLIGAVIAGRDFYKILGVPRASIKDIKKAYRKLALQLHPDRNPDD  
PQAQEKFDLGAAYEVLSDSEKRKQYDTYGEGLKDGHQSSHGDI FSHFFGDFGFMFGGT  
PRQQDRNIPRGSDIIVDLEVTLEEYVYAGNFVEVVRNKPVARQAPGKRKCNCRQEMRTTQL  
GPGRFQMTQEVVCDECPNVKLVNEERTLEVEIEPGVRDGMETPFGEGEPHVDGEPGDLR  
FRIKVVKHPIFERRGDDLYTNVTISLVESLVGFEMDITHLDGHKVHISRDKITRPGAKLW  
KKGEGLPNFDNNNIKGSLIITFDVDFPKEQLTEEAREGIKQLLKQGSVQKVYNGLQGY

**Important features:****Signal peptide:**

amino acids 1-22

**Cell attachment sequence:**

amino acids 254-257

**Nt-dnaJ domain signature:**

amino acids 67-87

**Homologous region to Nt-dnaJ domain proteins:**

amino acids 26-58

**N-glycosylation site:**

amino acids 5-9, 261-265

**Tyrosine kinase phosphorylation site:**

amino acids 253-260

**N-myristoylation site:**

amino acids 18-24, 31-37, 93-99, 215-221

**Amidation site:**

amino acids 164-168

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**FIGURE 105**

GGCACGAGGCGGCGGGGCAGTCGCGGGATGCGCCCGGAGCCACAGCCTGAGGCCCTCAG  
GTCTCTGCAGGTGTCGTGGAGGAACCTAGCACCTGCCATCCTCTTCCCCAATTTGCCACT  
TCCAGCAGCTTTAGCCCATGAGGAGGATGTGACCGGGACTGAGTCAGGAGCCCTCTGGAA  
GCATGGAGACTGTGGTGATTGTTGCCATAGGTGTGCTGGCCACCATCTTTCTGGCTTCGT  
TTGCAGCCTTGGTGCTGGTTTGCAGGCAGCGCTACTGCCGCGCGAGACCTGCTGCAGC  
GCTATGATTCTAAGCCCATTTGTGGACCTCATTGGTGCCATGGAGACCCAGTCTGAGCCCT  
CTGAGTTAGAACTGGACGATGTCGTTATCACCAACCCCCACATTGAGGCCATTCTGGAGA  
ATGAAGACTGGATCGAAGATGCCTCGGGTCTCATGTCCCACTGCATTGCCATCTTGAAGA  
TTTGTCACTCTGACAGAGAAGCTTGTTGCCATGACAATGGGCTCTGGGGCCAAGATGA  
AGACTTCAGCCAGTGTGACGACATCATTTGTGGTGGCCAAGCGGATCAGCCCCAGGGTGG  
ATGATGTTGTGAAGTCGATGTACCCTCCGTTGGACCCCCAACTCCTGGACGCACGGACGA  
CTGCCCTGCTCCTGTCTGTGAGTCACCTGGTGCTGGTGACAAGGAATGCCTGCCATCTGA  
CGGGAGGCCTGGACTGGATTGACCAGTCTCTGTGCGCTGCTGAGGAGCATTTGGAAGTCC  
TTCGAGAAGCAGCCCTAGCTTCTGAGCCAGATAAAGGCCTCCCAGGCCCTGAAGGCTTCC  
TGCAGGAGCAGTCTGCAATTTAGTGCCTACAGGCCAGCAGCTAGCCATGAAGGCCCTGC  
CGCCATCCCTGGATGGCTCAGCTTAGCCTTCTACTTTTTCTATAGAGTTAGTTGTTCTC  
CACGGCTGGAGAGTTCAGCTGTGTGTGCATAGTAAAGCAGGAGATCCCCGTCAGTTTATG  
CCTCTTTTGCAGTTGCAAACTGTGGCTGGTGAGTGAGTGGCAGTCTAATACTACAGTTAGGGGA  
GATGCCATTCACTCTCTGCAAGAGGAGTATTGAAAACCTGGTGGACTGTCAGCTTTATTTA  
GCTCACCTAGTGTTTTCAAGAAAATTGAGCCACCGTCTAAGAAATCAAGAGGTTTACAT  
TAAATTAGAATTTCTGGCCTCTCTCGATCGGTCAGAATGTGTGGCAATTCTGATCTGCA  
TTTTCAGAAGAGGACAATCAATTGAACTAAGTAGGGGTTTCTTCTTTTGGCAAGACTTG  
TACTCTCTCACCTGGCCTGTTTCATTTATTTGTATTATCTGCCTGGTCCCTGAGGCGTCT  
GGGTCTCTCCTCTCCCTTGACAGGTTTGGGTTTGAAGCTGAGGAACTACAAAGTTGATGAT  
TTCTTTTTTATCTTTATGCCTGCAATTTTACCTAGCTACCACTAGGTGGATAGTAAATTT  
ATACTTATGTTTCCCTCAAAAAAAAAAAAAA

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**FIGURE 106**

METVVIVAIGVLATIFLASFAALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPS  
ELELDDVVITNPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMK  
TSASVSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDARTTALLSVSHLVLVTRNACHLT  
GGLDWIDQSLSAAEHLEVLREAALASEPDKGLPGPEGFLQEQSAI



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**FIGURE 107**

GCTTCATTTCTCCCGACTCAGCTTCCCACCCCTGGGCTTTCCGAGGTGCTTTTCGCCGCTGT  
CCCCACCACTGCAGCCATGATCTCCTTAACGGACACGCAGAAAATTGGAATGGGATTAAC  
AGGATTTGGAGTGTTTTTCTGTTCTTTGGAATGATTCTCTTTTTTGACAAAGCACTACT  
GGCTATTGGAAATGTTTTATTTGTAGCCGGCTTGGCTTTTGTAATTGGTTTAGAAAGAAC  
ATTCAGATTCTTCTTCCAAAAACATAAAATGAAAGCTACAGGTTTTTTTCTGGGTGGTGT  
ATTTGTAGTCCTTATTGGTTGGCCTTTGATAGGCATGATCTTCGAAATTTATGGATTTTT  
TCTCTTGTTCAAGGGCTTCTTTCCTGTCGTTGTTGGCTTTATTAGAAGAGTGCCAGTCCT  
TGGATCCCTCCTAAATTTACCTGGAATTAGATCATTTGTAGATAAAGTTGGAGAAAGCAA  
CAATATGGTATAAACAACAAGTGAATTTGAAGACTCATTTAAAATATTGTGTTATTTATAA  
AGTCATTTGAAGAATATTCAGCACAAAATTAAATTACATGAAATAGCTTGTAATGTTCTT  
TACAGGAGTTTAAAACGTATAGCCTACAAAGTACCAGCAGCAAATTAGCAAAGAAGCAGT  
GAAAACAGGCTTCTACTCAAGTGAACCTAAGAAGAAGTCAGCAAGCAAAGTGAGAGAGGTG  
AAATCCATGTTAATGATGCTTAAGAACTCTTGAAGGCTATTTGTGTTGTTTTTCCACAA  
TGTGCGAACTCAGCCATCCTTAGAGAACTGTGGTGCCTGTTTCTTTTCTTTTATTTTG  
AAGGCTCAGGAGCATCCATAGGCATTTGCTTTTGTAGAAGTGCCACTGCAATGGCAAAAA  
TATTTCCAGTTGCACTGTATCTCTGGAAGTGATGCATGAATTCGATTGGATTGTGTCATT  
TTAAAGTATTAAAACCAAGGAAACCCCAATTTTGATGTATGGATTACTTTTTTTTGNGCN  
CAGGGCC

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**FIGURE 108**

MISLTDQTQKIGMGLTGFGVFFLFFGMILFFDKALLAIGNVLFVAGLAFVIGLERTFRFFF  
QKHKMKATGFFLGGVFVVLIGWPLIGMIFEIYGFFLLFRGFFPVVVGFIRRVFVLGSLLN  
LPGIRSFVDKVGESNNMV

**Important features:****Transmembrane domains:**

amino acids 12-30 (typeII), 33-52, 69-89 and 93-109

**N-myristoylation sites:**

amino acids 11-16, 51-56 and 116-121

**Aminoacyl-transfer RNA synthetases class-II protein:**

amino acids 49-59

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**FIGURE 109**

CCAGTCTGTCGCCACCTCACTTGGTGTCTGCTGTCCCCGCCAGGCAAGCCTGGGGTGAGA  
GCACAGAGGAGTGGGCCGGGACCATGCGGGGGACGCGGCTGGCGCTCCTGGCGCTGGTGC  
TGGCTGCCTGCGGAGAGCTGGCGCCGGCCCTGCGCTGCTACGTCTGTCCGGAGCCCACAG  
GAGTGTGCGACTGTGTCACCATCGCCACCTGCACCACCAACGAAACCATGTGCAAGACCA  
CACTCTACTCCCGGGAGATAGTGTACCCCTTCCAGGGGGACTCCACGGTGACCAAGTCCT  
GTGCCAGCAAGTGTAAGCCCTCGGATGTGGATGGCATCGGCCAGACCCTGCCCCTGTCCT  
GCTGCAATACTGAGCTGTGCAATGTAGACGGGGCGCCCGCTCTGAACAGCCTCCACTGCG  
GGGCCCTCACGCTCCTCCCACTCTTGAGCCTCCGACTGTAGAGTCCCCGCCACCCCCAT  
GGCCCTATGCGGCCAGCCCCGAATGCCTTGAAGAAGTGCCCCCTGCACCAGGAAAAAA  
AAAAA

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**FIGURE 110**

MRGTRLALLALVLAACGELAPALRCYVCPEPTGVSDCVTIATCTTNETMCKTTLYSREIV  
YPFQGDSTVTKSCASKCKPSDVDGIGQTLFVSCCNTELCNVDGAPALNSLHCGALTLLPL  
LSLRL

**Important features:**

**Signal peptide:**

amino acids 1-17

**N-glycosylation site:**

amino acids 46-49

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**FIGURE 111**

GCGCCGCCAGGCGTAGGCGGGGTGGCCCTTGCGTCTCCCGCTTCCTTGAAAAACCCGGCG  
GGCGAGCGAGGCTGCGGGCCGGCCGCTGCCCTTCCCCACACTCCCCGCCGAGAAGCCTCG  
CTCGGCGCCCAACATGGCGGGTGGGCGCTGCGGCCCGCAGCTAACGGCGCTCCTGGCCGC  
CTGGATCGCGGCTGTGGCGGCGACGGCAGGCCCCGAGGAGGCCGCGCTGCCGCCGGAGCA  
GAGCCGGGTCCAGCCCATGACCGCCTCCAACCTGGACGCTGGTGATGGAGGGCGAGTGGAT  
GCTGAAATTTTACGCCCCATGGTGTCCATCCTGCCAGCAGACTGATTCAGAATGGGAGGC  
TTTTGCAAAGAATGGTGAAATACCTCAGATCAGTGTGGGGAAGGTAGATGTCATTCAAGA  
ACCAGGTTTGAGTGGCCGCTTCTTTGTCACCACTCTCCAGCATTTTTTTCATGCAAAGGA  
TGGGATATTCCGCCGTTATCGTGGCCAGGAATCTTCGAAGACCTGCAGAATTATATCTT  
AGAGAAGAAATGGCAATCAGTCGAGCCTCTGACTGGCTGGAAATCCCCAGCTTCTCTAAC  
GATGCTCTGGAATGGCTGGTCTTTTTAGCATCTCTGGCAAGATATGGCATCTTCACAACTA  
TTTCACAGTGACTCTTGGAATTCCTGCTTGGTGTCTTATGTGTTTTTCGTCATAGCCAC  
CTTGGTTTTTTGGCCTTTTTATGGGTCTGGTCTTGGTGGTAATATCAGAATGTTTCTATGT  
GCCACTTCCAAGGCATTTATCTGAGCGTTCTGAGCAGAATCGGAGATCAGAGGAGGCTCA  
TAGAGCTGAACAGTTGCAGGATGCGGAGGAGGAAAAAGATGATTCAAATGAAGAAGAAAA  
CAAAGACAGCCTTGTAGATGATGAAGAAGAGAAAGAAGATCTTGGCGATGAGGATGAAGC  
AGAGGAAGAAGAGGAGGAGGACAACCTGGCTGCTGGTGTGGATGAGGAGAGAAGTGAGGC  
CAATGATCAGGGGGCCCCCAGGAGAGGACGGTGTGACCCGGGAGGAAGTAGAGCCTGAGGA  
GGCTGAAGAAGGCATCTCTGAGCAACCCTGCCAGCTGACACAGAGGTGGTGGAAAGACTC  
CTTGAGGCAGCGTAAAAGTCAGCATGCTGACAAGGGACTGTAGATTTAATGATGCGTTTTT  
CAAGAATACACACCAAAACAATATGTCAGCTTCCCTTTGGCCTGCAGTTTGTACCAAATC  
CTTAATTTTTTCTGAATGAGCAAGCTTCTCTTAAAAGATGCTCTCTAGTCATTTGGTCTC  
ATGGCAGTAAGCCTCATGTATACTAAGGAGAGTCTTCCAGGTGTGACAATCAGGATATAG  
AAAAACAAACGTAGTGTTGGGATCTGTTTTGGAGACTGGGATGGGAACAAGTTCATTTACT  
TAGGGGTGAGAGAGTCTCGACCAGAGGAGGCCATTTCCAGTCCTAATCAGCACCTTCCAG  
AGACAAGGCTGCAGGCCCTGTGAAATGAAAGCCAAGCAGGAGCCTTGGCTCCTGAGCATC  
CCCAAAGTGTAACGTAGAAGCCTTGCATCCTTTTCTTGTGTAAAGTATTTATTTTTGTCA  
AATTGCAGGAAACATCAGGCACCACAGTGCATGAAAAATCTTTCACAGCTAGAAATTGAA  
AGGGCCTTGGGTATAGAGAGCAGCTCAGAAGTCATCCAGCCCTCTGAATCTCCTGTGCT  
ATGTTTTATTTCTTACCTTTAATTTTTCCAGCATTTCCACCATGGGCATTCAGGCTCTCC  
ACACTCTTCACTATTATCTCTTGGTCAGAGGACTCCAATAACAGCCAGGTTTACATGAAC  
TGACTGCCAAACATCTCAAATGAAATGTTGTGGCCATCAGAGACTCAAAGGAAGTAAG  
GATTTTACAAGACAGATTAAAAAAAATTGTTTTGTCCAAATATAGTTGTTGTTGATTT  
TTTTTTAAGTTTTCTAAGCAATATTTTTCAAGCCAGAAGTCCTCTAAGTCTTGCCAGTAC  
AAGGTAGTCTTGTGAAGAAAAGTTGAATACTGTTTTGTTTTCATCTCAAGGGGTTCCCTG  
GGTCTTGAACACTTTAATAATAACTAAAAAACCACTTCTGATTTTCTTCAAGTGATGTG  
CTTTTGGTGAAAGAATTAATGAACTCCAGTACCTGAAAGTGAAAGATTTGATTTTGTTC  
CATCTTCTGTAATCTTCCAAAGAATTATCTTTGTAAATCTCTCAATACTCAATCTACT  
GTAAGTACCCAGGGAGGCTAATTTCTTT

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**FIGURE 112**

MAGGRCGPQLTALLAAWIAAVAATAGPEEAALPPEQSRVQPMTASNWTLVMEGEWMLKFY  
APWCPSCQQTDSWEAFAKNGEILQISVGKVDVIQEPGLSGRFFVTTLPAFFHAKDGI FR  
RYRGP G IFEDLQNYILEKKWQSVEPLTGWKSPASLTMSGMAGLFSISGKIWHLHNYFTVT  
LGIPAWCSYVFFVIATLVFGLFMGLVLVVISSECFYVPLPRHLSERSEQNRRSEEAHRAEQ  
LQDAEEEKDDSNEEENKDSLVDDEEEKEDLGDEDEAEEDNLAAGVDEERSEANDQG  
PPGEDGVTREEVEPEEAEEGISEQPCPADTEVVEDSLRQRKSQHADKGL

**Important features:****Signal peptide:**

amino acids 1-22

**Transmembrane domain:**

amino acids 191-211

**N-glycosylation site:**

amino acids 46-49

**Thioredoxin family proteins:** (homologous region to disulfide  
isomerase)

amino acids 56-72

**Flavodoxin proteins:**

amino acids 173-187

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**FIGURE 113**

GAGGAACCTACCGGTACCGGCCGCGCGCTGGTAGTCGCCGGTGTGGCTGCACCTCACCAA  
TCCCGTGCGCCGCGGCTGGGCCGTCGGAGAGTGCCTGTGCTTCTCTCCTGCACGCGGTGC  
TTGGGCTCGGCCAGGCGGGTCCGCCGCCAGGGTTTGAGGATGGGGAGTAGCTACAGGA  
AGCGACCCCGCGATGGCAAGGTATATTTTTGTGGAATGAAAAGGAAGTATTAGAAATGAG  
CTGAAGACCATTACAGATTAATATTTTTGGGGACAGATTTGTGATGCTTGATTCACCCCT  
TGAAGTAATGTAGACAGAAGTTCTCAAATTTGCATATTACATCAACTGGAACCAGCAGTG  
AATCTTAATGTTCACTTAAATCAGAACTTGCATAAGAAAGAGAATGGGAGTCTGGTTAAA  
TAAAGATGACTATATCAGAGACTTGAAAAGGATCATTCTCTGTTTTCTGATAGTGTATAT  
GGCCATTTTAGTGGGCACAGATCAGGATTTTTACAGTTTACTTGGAGTGTCCAAAACCTGC  
AAGCAGTAGAGAAATAAGACAAGCTTTCAAGAAATTGGCATTGAAGTTACATCCTGATAA  
AAACCCGAATAACCCAAATGCACATGGCGATTTTTTAAAAATAAATAGAGCATATGAAGT  
ACTCAAAGATGAAGATCTACGGAAAAAGTATGACAAATATGGAGAAAAGGGACTTGAGGA  
TAATCAAGGTGGCCAGTATGAAAGCTGGAACATTATCGTTATGATTTTGGTATTTATGA  
TGATGATCCTGAAATCATAACATTGGAAAGAAGAGAATTTGATGCTGCTGTTAATTCTGG  
AGAACTGTGGTTTGTAATTTTTACTCCCCAGGCTGTTCACTGCCATGATTTAGCTCC  
CACATGGAGAGACTTTGCTAAAGAAGTGGATGGGTACTTCGAATTGGAGCTGTAACTG  
TGGTGTATGATAGAATGCTTTGCCGAATGAAAGGAGTCAACAGCTATCCAGTCTCTTCAT  
TTTTCGGTCTGGAATGGCCCCAGTGAAATATCATGGAGACAGATCAAAGGAGAGTTTTAGT  
GAGTTTTGCAATGCAGCATGTTAGAAGTACAGTGACAGAACTTTGGACAGGAAATTTTTGT  
CAACTCCATACAACTGCTTTTGCTGCTGGTATTGGCTGGCTGATCACTTTTTGTTCAAA  
AGGAGGAGATTGTTTGACTTCACAGACACGACTCAGGCTTAGTGGCATGTTGTTTTCTCAA  
CTCATTGGATGCTAAAGAAATATATTTGGAAGTAATACATAATCTTCCAGATTTTGAAC  
ACTTTTCGGCAAACACACTAGAGGATCGTTTGGCTCATCATCGGTGGCTGTTATTTTTTCA  
TTTTGGAAAAAATGAAAATTCAAATGATCCTGAGCTGAAAAAACTAAAACTCTACTTAA  
AAATGATCATATTCAAGTTGGCAGGTTTGACTGTTCCCTCTGCACCAGACATCTGTAGTAA  
TCTGTATGTTTTTTCAGCCGTCTCTAGCAGTATTTAAAGGACAAGGAACCAAAGAATATGA  
AATTCATCATGGAAAGAAGATTCTATATGATATACTTGCCTTTGCCAAAGAAAGTGTGAA  
TTCTCATGTTACCACGCTTGGACCTCAAAATTTTTCTGCCAATGACAAAGAACCATGGCT  
TGTTGATTTCTTTGCCCCCTGGTGTCCACCATGTGAGCTTTACTACCAGAGTTACGAAG  
AGCATCAAATCTTCTTTATGGTCAGCTTAAAGTTTGGTACACTAGATTGTACAGTTCATGA  
GGGACTCTGTAAACATGTATAACATTCAAGGCTTATCCAACAACAGTGGTATTCAACCAGTC  
CAACATTCATGAGTATGAAGGACATCACTCTGCTGAACAAATCTTGGAGTTCATAGAGGA  
TCTTATGAATCCTTCAGTGGTCTCCCTTACACCCACCACCTTCAACGAACCTAGTTACACA  
AAGAAAACACAACGAAGTCTGGATGGTTGATTCTATTCTCCGTGGTGTATCCTTGCCA  
AGTCTTAATGCCAGAATGGAAAAGAATGGCCCGGACATTAAGTGGACTGATCAACGTGGG  
CAGTATAGATTGCCAACAGTATCATTCTTTTTGTGCCAGGAAAACGTTCAAAGATACCC  
TGAGATAAGATTTTTTCCCCCAAATCAAATAAAGCTTATCAGTATCACAGTTACAATGG  
TTGGAATAGGGATGCTTATTCCTGAGAATCTGGGGTCTAGGATTTTTTACCTCAAGTATC  
CACAGATCTAACACCTCAGACTTTTCAGTGAAAAAGTTCTACAAGGGAAAAATCATTGGGT  
GATTGATTTCTATGCTCCTTGGTGTGGACCTTGCCAGAATTTTGCTCCAGAATTTGAGCT  
CTTGGCTAGGATGATTAAAGGAAAAGTGAAAGCTGGAAAAGTAGACTGTCAGGCTTATGC  
TCAGACATGCCAGAAAGCTGGGATCAGGGCTATCCAAGTGAAGTTTATTTCTACGA  
AAGAGCAAAGAGAAATTTTTCAAGAAGAGCAGATAAATACCAGAGATGCAAAGCAATCGC  
TGCCTTAATAAGTGAAAAATTGAAAACCTCTCCGAAATCAAGGCAAGAGGAATAAGGATGA  
ACTTTGATAATGTTGAAGATGAAGAAAAAGTTTAAAAAGAAATCTGACAGATGACATCAG  
AAGACACCTATTTAGAATGTTACATTTATGATGGGAATGAATGAACATTATCTTAGACTT

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GCAGTTGTTACTGCCAGAATTATCTACAGCACTGGTGTAAAAGAAGGGTCTGCAAACCTTTT  
TCTGTAAAGGGCCGGTTTATAAATATTTTAGACTTTGCAGGCTATAATATATGGTTCACA  
CATGAGAACAAGAATAGAGTCATCATGTATTCTTTGTTATTTGCTTTTAAACAACCTTTAA  
AAAATATTTAAACGATTCTTAGCTCAGAGCCATACAAAAGTAGGCTGGATTCAGTCCATG  
GACCATAGATTGCTGTCCCCCTCGACGGACTTATAATGTTTCAGGTGGCTGGCTTGAACA  
TGAGTCTGCTGTGCTATCTACATAAATGTCTAAGTTGTATAAAGTCCACTTTCCTTCAC  
GTTTTTTGGCTGACCTGAAAAGAGGTAACTTAGTTTTTTGGTCACTTGTTCTCCTAAAAAT  
GCTATCCCTAACCATATATTTATATTTTCGTTTTAAAAACACCCATGATGTGGCACAGTAA  
ACAAACCCTGTTATGCTGTATTATTATGAGGAGATTCTTCATTGTTTTCTTTCCTTCTCA  
AAGGTTGAAAAAATGCTTTTAAATTTTTTACAGCCGAGAAACAGTGCAGCAGTATATGTGC  
ACACAGTAAGTACACAAATTTGAGCAACAGTAAGTGCACAAATTCTGTAGTTTGCTGTAT  
CATCCAGGAAAACCTGAGGGAAAAAAATTATAGCAATTAAGTGGGCATTGTAGAGTATCC  
TAAATATGTTATCAAGTATTTAGAGTTCTATATTTTAAAGATATATGTGTTTCATGTATTT  
TCTGAAATTGCTTTCATAGAAATTTTCCCCTGATAGTTGATTTTTTGAGGCATCTAATAT  
TTACATATTTGCCTTCTGAACTTTGTTTTGACCTGTATCCTTTATTTACATTGGGTTTTT  
CTTTCATAGTTTTTGGTTTTTCACTCCTGTCCAGTCTATTTATTATTCAAATAGGAAAAAT  
TACTTTACAGGTTGTTTTACTGTAGCTTATAATGATACTGTAGTTATTCCAGTTACTAGT  
TTACTGTCAGAGGGCTGCCTTTTTTTCAGATAAATATTGACATAATAACTGAAGTTATTTTT  
ATAAGAAAATCAAGTATATAAATCTAGGAAAGGGATCTTCTAGTTTCTGTGTTGTTTAGA  
CTCAAAGAATCACAAATTTGTCAGTAACATGTAGTTGTTTAGTTATAATTTCAGAGTGTAC  
AGAATGGTAAAAATTCCAATCAGTCAAAAGAGGTCAATGAATTAAAAGGCTTGCAACTTT  
TTCAAAAAAAAAAAAAAAAAA



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**FIGURE 114**

MGVWLNKDDYIRD LKRIILCFLIVYMAILVGT DQDFYSL LGVSKTASSREIRQAFKKLAL  
KLHPDKNPNNPNAHGDF LKINRAYEVLKDEDLRKKYDKYGEK GLEDNQGGQYESWNYRY  
DFGIYDDDPEIITLERREFDA AVNSGELW FVNFYSPGCSHCHDLAPTWRDFAKEVDGLLR  
IGAVNCGDDRMLCRMKG VNSYPSLFIFRSGMAPVKYHGDRSKESLV SFAMQHVRSTVTEL  
WTGNFVNSIQTAFAAGIGWLITFCSKGGDCLTSQTRLRLSGMLF LNSLDAKEIYLEVIHN  
LPDFELLSANTLEDRLA HHRWLLFFHFGKNENSNDPELKKLKTLLKNDHIQVGRFDCSSA  
PDICSNLYVFQPSLAVFKGQGTKEYEIH HGKKILYDILAFAKESVNSHVTTLGPNFPAN  
DKEPWLVDFFAPWCPPCRALLPELRRASNLLYGQLKFGTLDCTVHEGLCNMYNIQAYPTT  
VVFNQSNIEHEYEGHSAEQILEFIEDLMNPSVVSLTPTTFNELVTQRKHNEVWMVDFYSP  
WCHPCQVLMPEWKRMARTLTGLINVGSIDCQQYHSFCAQENVQRYPEIRFFPPKSNKAYQ  
YHSYNGWNRDAYSLRIWGLGFLPQVSTD LTPQTFSEKVLQGKNHWVIDFYAPWCGPCQNF  
APEFELLARMIKGVKAGKVDCQAYAQTCQKAGIRAYPTVKFYFYERAKRNFQEEQINTR  
DAKAIAALISEKLETLRNQGRNKDEL

**Important features:**

**Endoplasmic reticulum targeting sequence:**

amino acids 744-747

**Cytochrome c family heme-binding site signature:**

amino acids 158-163

**Nt-dnaJ domain signature:**

amino acids 77-96

**N-glycosylation site:**

amino acids 484-487

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**FIGURE 115**

GCGGGCTGTTGACGGCGCTGCGATGGCTGCCTGCGAGGGCAGGAGAAGCGGAGCTCTCGG  
TTCCTCTCAGTCGGACTTCCTGACGCCGCCAGTGGGCGGGGCCCCCTTGGGCCGTCGCCAC  
CACTGTAGTCATGTACCCACCGCCGCCGCCGCCCTCATCGGGACTTCATCTCGGTGAC  
GCTGAGCTTTGGCGAGAGCTATGACAACAGCAAGAGTTGGCGGGCGGCGCTCGTGCTGGAG  
GAAATGGAAGCAACTGTGCGAGATTGCAGCGGAATATGATTCTCTTCTCCTTGCCTTTCT  
GCTTTTCTGTGGACTCCTCTTCTACATCAACTTGGCTGACCATTGGAAAGCTCTGGCTTT  
CAGGCTAGAGGAAGAGCAGAAGATGAGGCCAGAAATTGCTGGGTTAAAACCAGCAAATCC  
ACCCGTCTTACCAGCTCCTCAGAAGGCGGACACCCGACCCTGAGAACTTACCTGAGATTTC  
GTCACAGAAGACACAAAGACACATCCAGCGGGGACCACCTCACCTGCAGATTAGACCCCC  
AAGCCAAGACCTGAAGGATGGGACCCAGGAGGAGGCCACAAAAGGCAAGAAGCCCCCTGT  
GGATCCCCGCCCGGAAGGAGATCCGCAGAGGACAGTCATCAGCTGGAGGGGAGCGGTGAT  
CGAGCCTGAGCAGGGCACCGAGCTCCCTTCAAGAAGAGCAGAAGTGCCACCAAGCCTCC  
CCTGCCACCGGCCAGGACACAGGGCACACCAAGTGCATCTGAACATATCGCCAGAAGGGCGT  
GATTGACGTCTTCTGTCATGCATGGAAGGATAACCGCAAGTTTGCATGGGGCCATGACGA  
GCTGAAGCCTGTGTCCAGGTCTTCAAGTGGTGGTGGCTCGGTCTCACACTGATCGA  
CGCGCTGGACACCATGTGGATCTTGGGTCTGAGGAAAGAATTTGAGGAAGCCAGGAAGTG  
GGTGTGGAAGAAGTTACACTTTGAAAAGGACGTGGACGTCAACCTGTTTGAGAGCACGAT  
CCGCATCCTGGGGGGGCTCCTGAGTGCCTACCACCTGTCTGGGGACAGCCTCTTCTGAG  
GAAAGCTGAGGATTTTGGAATCGGCTAATGCCTGCCTTCAGAACACCATCCAAGATTCC  
TTACTCGGATGTGAACATCGGTACTGGAGTTGCCCCACCGCCACGGTGGACCTCCGACAG  
CACTGTGGCCGAGGTGACCAGCATTAGCTGGAGTTCCGGGAGCTCTCCCGTCTCACAGG  
GGATAAGAAGTTTCAGGAGGCAGTGGAGAAGGTGACACAGCACATCCACGGCCTGTCTGG  
GAAGAAGGATGGGCTGGTGCCCATGTTTCAATACCCACAGTGGCCTCTTACCCACCT  
GGGCGTATTACGCTGGGCGCCAGGGCCGACAGCTACTATGAGTACCTGCTGAAGCAGTG  
GATCCAGGGCGGGAAGCAGGAGACACAGCTGCTGGAAGACTACGTGGAAGCCATCGAGGG  
TGTCAGAACGCACCTGCTGCGGCACTCCGAGCCCAGTAAGCTCACCTTTGTGGGGGAGCT  
TGCCACCGCCGCTTCAGTGCCAAGATGGACCACCTGGTGTGCTTCTGCCAGGGACGCT  
GGCTCTGGGCGTCTACCACGGCCTGCCCGCCAGCCACATGGAGCTGGCCAGGAGCTCAT  
GGAGACTTGTACCAGATGAACCGGCAGATGGAGACGGGGCTGAGTCCCGAGATCGTGCA  
CTTCAACCTTTACCCCCAGCCGGGCCGTCGGGACGTGGAGGTCAAGCCAGCAGACAGGCA  
CAACCTGCTGCGGCCAGAGACCGTGGAGAGCCTGTTCTACCTGTACCGCGTCACAGGGGA  
CCGCAAATACCAGGACTGGGGCTGGGAGATTCTGCAGAGCTTCAGCCGATTACACGGGT  
CCCCCTCGGGTGGCTATTCTTCCATCAACAATGTCCAGGATCCTCAGAAGCCCGAGCCTAG  
GGACAAGATGGAGAGCTTCTTCTGGGGGAGACGCTCAAGTATCTGTTCTTGCTCTTCTC  
CGATGACCCAAACCTGCTCAGCCTGGACGCCTACGTGTTCAACACCGAAGCCCACCCTCT  
GCCTATCTGGACCCCTGCCAGGGTGGATGGCTGCTGGTGTGGGACTTCGGGTGGGCAG  
AGGCACCTTGCTGGGTCTGTGGCATTTTCCAAGGGCCACGTCAGCACCGGCAACCGCCAA  
GTGCCCAGGCTCTGAACCTGGCTCTGGGCTCCTCCTCGTCTCTGCTTTAATCAGGACACC  
GTGAGGACAAGTGAGGCCGTCAGTCTTGGTGTGATGCGGGGTGGGCTGGGCCGCTGGAGC  
CTCCGCTGCTTCTCCAGAAGACACGAATCATGACTCACGATTGCTGAAGCCTGAGCAG  
GTCTCTGTGGGCCGACCAGAGGGGGGCTTCGAGGTGGTCCCTGGTACTGGGGTGACCGAG  
TGGACAGCCAGGGTGCAGCTCTGCCCGGGCTCGTGAAGCCTCAGATGTCCCAATCCAA  
GGGTCTGGAGGGGCTGCCGTGACTCCAGAGGCCTGAGGCTCCAGGGCTGGCTCTGGTGT  
TACAAGCTGGACTCAGGGATCCTCCTGGCCGCCCCGAGGGGGCTTGGAGGGCTGGACGG  
CAAGTCCGTCTAGCTCACGGGCCCTCCAGTGGAAATGGGTCTTTTCGGTGGAGATAAAAG  
TTGATTTGCTCTAACCGCAA

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**FIGURE 116**

MAACEGRRSGALGSSQSDFLTPPVGGAPWAVATTVMYPPPPPPPHRDFISVTLSFGESY  
DNSKSWRRRSCWRKWKQLSRLQRNMILFLLAFLFLFCGLLFYINLADHWKALAFRLEEEQK  
MRPEIAGLKPANPPVLPAPQKADTDPENLPEISSQKTQRHIQRGPPHLQIRPPSQDLKDG  
TQEEATKRQEAPVDPRPEGDPQRTVISWRGAVIEPEQGTELPSSRAEVPTKPPLPPARTQ  
GTPVHLNRYRQKGVIDVFLHAWKGYRKFAWGHDELKPVSRSFSEWFGLGLTLIDALDTMWI  
LGLRKEFEEARKWVSKKLHFEDVDVNLFEISTIRILGGLLSAYHLSGDSLFRLKAEDFGN  
RLMPAFRTPSKIPYSDVNIGTGVAHPPRWTS DSTVAEVT SIQLEFRELSRLTGDKKFQEA  
VEKVTQHIHGLSGKKDGLVPMFINTHSGLFTHLGVFTLGARADSYEYLLKQWIQGGKQE  
TQLLEDYVEAIEGVRTHLLRHSEPSKLT FVGELAHGRFSAKMDHLVCFLPGTLALGVYHG  
LPASHMELAQELMETCYQMNROMETGLSPEIVHFNLYPQGRRDVEVKPADRHNLRLPET  
VESLFYLYRVTGDRKYQDWGWEILQSFSRFRTRVPSGGYSSINNVQDPQKPEPRDKMESFF  
LGETLKYLFLFLFSDDPNLLSLDAYVFNTAHPLPIWTPA

**Important features of the protein:**

**Transmembrane domain:**

amino acids 21-40 and 84-105 (type II)

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**FIGURE 117**

GTGGGATTTATTTGAGTGCAAGATCGTTTTCTCAGTGGTGGTGGAAAGTTGCCTCATCGCA  
GGCAGATGTTGGGGCTTTGTCCGAACAGCTCCCCCTCTGCCAGCTTCTGTAGATAAGGGTT  
AAAACTAATATTTATATGACAGAAGAAAAAGATGTCATTCCGTAAAGTAAACATCATCA  
TCTTGGTCCTGGCTGTTGCTCTCTTCTTACTGGTTTTTGCACCATAACTTCCTCAGCTTGA  
GCAGTTTGTAAAGGAATGAGGTTACAGATTCAGGAATTGTAGGGCCTCAACCTATAGACT  
TTGTCCCAAATGCTCTCCGACATGCAGTAGATGGGAGACAAGAGGAGATTCTGTGGTCA  
TCGCTGCATCTGAAGACAGGCTTGGGGGGGCCATTGCAGCTATAAACAGCATTCAGCACA  
ACACTCGCTCCAATGTGATTTTCTACATTGTTACTCTCAACAATACAGCAGACCATCTCC  
GGTCCTGGCTCAACAGTGATTCCCTGAAAAGCATCAGATACAAAATTGTCAATTTTGACC  
CTAAACTTTTGGAAGGAAAAGTAAAGGAGGATCTGACCAGGGGGAATCCATGAAACCTT  
TAACCTTTGCAAGGTTCTACTTGCCAATTCTGGTTCCCAGCGCAAAGAAGGCCATATACA  
TGGATGATGATGTAATTGTGCAAGGTGATATCTTGCCCTTTACAATACAGCACTGAAGC  
CAGGACATGCAGCTGCATTTTTCAGAAGATTGTGATTTCAGCCTCTACTAAAGTTGTCATCC  
GTGGAGCAGGAAACCAGTACAATTACATTGGCTATCTTGACTATAAAAAGGAAAGAATTC  
GTAAGCTTTCCATGAAAGCCAGCACTTGCTCATTTAATCCTGGAGTTTTTGTGCAAACC  
TGACGGAATGGAAACGACAGAATATAACTAACCAACTGGAAAAATGGATGAAACTCAATG  
TAGAAGAGGGACTGTATAGCAGAACCTGGCTGGTAGCATCACAAACACCTCCTCTGCTTA  
TCGTATTTTATCAACAGCACTCTACCATCGATCCTATGTGGAATGTCCGCCACCTTGTT  
CCAGTGCTGGAAAACGATATTCACCTCAGTTTGTAAAGGCTGCCAAGTTACTCCATTGGA  
ATGGACATTTGAAGCCATGGGGAAGGACTGCTTCATATACTGATGTTTGGGAAAAATGGT  
ATATTCCAGACCCAACAGGCAAATTC AACCTAATCCGAAGATATAACCGAGATCTCAAACA  
TAAAGTGAAACAGAATTTGAACTGTAAGCAAGCATTTCTCAGGAAGTCCTGGAAGATAGC  
ATGCATGGGAAGTAACAGTTGCTAGGCTTCAATGCCTATCGGTAGCAAGCCATGGAAAAA  
GATGTGTCAGCTAGGTAAAGATGACAAACTGCCCTGTCTGGCAGTCAGCTTCCCAGACAG  
ACTATAGACTATAAATATGTCTCCATCTGCCTTACCAAGTGTTTTCTTACTACAATGCTG  
AATGACTGGAAAGAAGAACTGATATGGCTAGTTTCAGCTAGCTGGTACAGATAATTCAAAA  
CTGCTGTTGGTTTTAATTTTGTAACCTGTGGCCTGATCTGTAAATAAACTTACATTTTTC

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**FIGURE 118**

MSFRKVNIIILVLAVALFLLVLHHNFLSLSSLLRNEVTD SGIVGPQPIDFVPNALRHAVD  
GRQEEIPVVIAASEDRLGGAIAAINSIQHNTRSNVIFYIVTLNNTADHLRSWLNSDSLKS  
IRYKIVNFDPKLLEGKVKEDPDQGESMKPLTFARFYLPILVPSAKKAIYMDDDVIVQGDI  
LALYNTALKPGHAAAFSEDCDSASTKVVIRGAGNQYNYIGYLDYKKERIRKLSMKASTCS  
FNPGVFVANLTEWKRQNI TNQLEKWMKLNVEEGLYSRTLGSITTPPLLIVFYQQHSTID  
PMWNVRLGSSAGKRYSPQFVKAALLHWNGHLKPWGRTASYTDVWEKWYIPDPTGKFNL  
IRRYTEISNIK

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**FIGURE 119**

CCATCCCTGAGATCTTTTTATAAAAAACCCAGTCTTTGCTGACCAGACAAAGCATACCAG  
ATCTCACCAGAGAGTCGCAGACACTATGCTGCCTCCCATGGCCCTGCCCAGTGTGTCCTG  
GATGCTGCTTTCTGCCTCATTCTCCTGTGTCAAGGTGAAGAAACCCAGAAGGA  
ACTGCCCTCTCCACGGATCAGCTGTCCCAAAGGCTCCAAGGCCTATGGCTCCCCCTGCTA  
TGCCTTGTTTTTGTACCAAAATCCTGGATGGATGCAGATCTGGCTTGCCAGAAGCGGCC  
CTCTGGAAACTGGTGTCTGTGCTCAGTGGGGCTGAGGGATCCTTCGTGTCCTCCCTGGT  
GAGGAGCATTAGTAACAGCTACTCATACATCTGGATTGGGCTCCATGACCCACACAGGG  
CTCTGAGCCTGATGGAGATGGATGGGAGTGGAGTAGCACTGATGTGATGAATTACTTTGC  
ATGGGAGAAAAATCCCTCCACCATCTTAAACCCTGGCCACTGTGGGAGCCTGTCAAGAAG  
CACAGGATTTCTGAAGTGGAAAGATTATAACTGTGATGCAAAGTTACCCTATGTCTGCAA  
GTTCAAGGACTAGGGCAGGTGGGAAGTCAGCAGCCTCAGCTTGGCGTGCAGCTCATCATG  
GACATGAGACCAGTGTGAAGACTCACCCCTGGAAGAGAATATTCTCCCCAACTGCCCTAC  
CTGACTACCTTGTCATGATCCTCCTTCTTTTTCTTTTTCTTCACCTTCATTTCAAGGCTT  
TTCTCTGTCTTCCATGTCTTGAGATCTCAGAGAATAATAATAAAAAATGTTACTTTATAAA  
AAAAAAAAAAAAAAAAAAAA

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**FIGURE 120**

MLPPMALPSVSWMLLSCLILLCQVQGEETQKELPSPRISCPKGSKAYGSPCYALFLSPKS  
WMDADLACQKRPSGKLVSLSGAEGSFVSSLVRSISNSYSYIWIGLHDPTQGSEPDGDGW  
EWSSTDVMNYFAWEKNPSTILNPGHCGSLSRSTGFLKWKDYNCDAKLPYVCKFKD

**Important features:**

**Signal peptide:**

amino acids 1-26

**C-type lectin domain signature:**

amino acids 146-171

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**FIGURE 121**

AAAGTTACATTTTCTCTGGAACCTCTCCTAGGCCACTCCCTGCTGATGCAACATCTGGGTT  
TGGGCAGAAAGGAGGGTGCTTCGGAGCCCCGCCCTTTCTGAGCTTCCTGGGCCGGCTCTAG  
ACAATTCAGGCTTCGCTGCGACTCAGACCTCAGCTCCAACATATGCATTCTGAAGAAAG  
ATGGCTGAGATGGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGGTCAAACCTGA  
GTCTACCAAATGCAGACTTTTACAATGGTTCTAGAAGAAATCTGGACAAGTCTTTTCATG  
TGGTTTTTCTACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGCCTGCC  
CCTCAGAACCTCTCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCAGTG  
ATCGCGCCTGGAGAAACAGTGTACTATTCTGTCTGAATACCAGGGGGAGTACGAGAGCCTG  
TACACGAGCCACATCTGGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCTGAGTGT  
GATGTCACTGATGACATCACGGCCACTGTGCCATACAACCTTCGTGTCAGGGCCACATTG  
GGCTCACAGACCTCAGCCTGGAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATC  
CTTACCCGACCTGGGATGGAGATCACCAAAGATGGCTTCCACCTGGTTATTGAGCTGGAG  
GACCTGGGGCCCCAGTTTGAGTTCCTTGTGGCCTACTGGAGGAGGGAGCCTGGTGCCGAG  
GAACATGTCAAAATGGTGAGGAGTGGGGGTATTCCAGTGCACCTAGAAACCATGGAGCCA  
GGGGCTGCATACTGTGTGAAGGCCAGACATTCGTGAAGGCCATTGGGAGGTACAGCGCC  
TTCAGCCAGACAGAATGTGTGGAGGTGCAAGGAGAGGCCATTCCCCTGGTACTGGCCCTG  
TTTGCCCTTTGTTGGCTTCATGCTGATCCTTGTGGTTCGTGCCACTGTTTCGTCTGAAAAATG  
GGCCGGCTGCTCCAGTACTCCTGTTGCCCGTGGTGGTCTCCAGACACCTTGAAAATA  
ACCAATTCACCCAGAAAGTTAATCAGCTGCAGAAGGGAGGAGGTGGATGCCTGTGCCACG  
GCTGTGATGTCTCCTGAGGAACCTCTCAGGGCCTGGATCTCATAGGTTTGCGGAAGGGCC  
CAGGTGAAGCCGAGAACCTGGTCTGCATGACATGGAAACCATGAGGGGACAAGTTGTGTT  
TCTGTTTTCCGCCACGGACAAGGGATGAGAGAAGTAGGAAGAGCCTGTTGTCTACAAGTC  
TAGAAGCAACCATCAGAGGCAGGGTGGTTTGTCTAACAGAACTGACTGAGGCTTAGGG  
GATGTGACCTCTAGACTGGGGGCTGCCACTTGCTGGCTGAGCAACCCTGGGAAAAGTGAC  
TTCATCCCTTCGGTCCTAAGTTTTCTCATCTGTAATGGGGGAATTACCTACACACCTGCT  
AAACACACACACACAGAGTCTCTCTATATATACACACGTACACATAAATACACCCAGC  
ACTTGCAAGGCTAGAGGGAACTGGTGACACTCTACAGTCTGACTGATTCACTGTTTCTG  
GAGAGCAGGACATAAATGTATGATGAGAATGATCAAGGACTCTACACACTGGGTGGCTTG  
GAGAGCCCACTTTCCAGAAATAATCCTTGAGAGAAAAGGAATCATGGGAGCAATGGTGT  
GAGTTCACCTCAAGCCCAATGCCGGTGCAGAGGGGAATGGCTTAGCGAGCTCTACAGTAG  
GTGACCTGGAGGAAGGTACAGCCCACTGAAAATGGGATGTGCATGAACACGGAGGATC  
CATGAACTACTGTAAAGTGTGACAGTGTGTGCACACTGCAGACAGCAGGTGAAATGTAT  
GTGTGCAATGCGACGAGAATGCAGAAGTCAGTAACATGTGCATGTTTGTGTGCTCCTTT  
TTTCTGTTGGTAAAGTACAGAATTCAGCAAATAAAAAGGGCCACCCTGGCCAAAAGCGGT  
AAAAAAAAAAAAAAAA



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**FIGURE 122**

MQTFTMVLEEIWTSLFMWFFYALIPCLLTDEVAILPAPQNLSVLSTNMKHLMLWSPVIAP  
GETVYYSVEYQGEYESLYTSHIWIPSSWCSLTEGPECDVTDDITATVPYNLRVRATLGSQ  
TSAWSILKHFPNRRNSTILTRPGMEITKDG FHLVIELEDLGPQFEFLVAYWRREPGEAEHV  
KMVRSGGIPVHLETMEPGAAYCVKAQTFVKAIGRYSAFSQTECVEVQGEAIPVLALFAF  
VGFMLILVVVPLFVWKMGRLQLYSCCPVVVLPDTLKITNSPQKLISCRREEVDACATAVM  
SPEELLRAWIS

**Important features:****Signal peptide:**

amino acids 1-29

**Transmembrane domain:**

amino acids 230-255

**N-glycosylation sites:**

amino acids 40-43 and 134-137

**Tissue factor proteins homology:**

amino acids 92-119

**Integrins alpha chain protein homology:**

amino acids 232-262

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**FIGURE 123**

CGGACGCGTGGGCGCCACCTCCGGAACAAGCCATGGTGGCGGCGACGGTGGCAGCGGCG  
TGGCTGCTCCTGTGGGCTGCGGCCTGCGCGCAGCAGGAGCAGGACTTCTACGACTTCAAG  
GCGGTCAACATCCGGGGCAAACCTGGTGTGCTGGAGAAGTACCGCGGATCGGTGTCCCTG  
GTGGTGAATGTGGCCAGCGAGTGGGCTTCACAGACCAGCACTACCGAGCCCTGCAGCAG  
CTGCAGCGAGACCTGGGCCCCCACCCTTTAACGTGCTCGCCTTCCCCTGCAACCAGTTT  
GGCCAACAGGAGCCTGACAGCAACAAGGAGATTGAGAGCTTTGCCCCCGCACCTACAGT  
GTCTCATTCCCCATGTTTAGCAAGATTGCAGTCACCGGTACTGGTGCCCATCCTGCCTTC  
AAGTACCTGGCCCAGACTTCTGGGAAGGAGCCCACCTGGAACCTTCTGGAAGTACCTAGTA  
GCCCCAGATGGAAAGGTGGTAGGGGCTTGGGACCCAACCTGTGTCAGTGGAGGAGGTCAGA  
CCCCAGATCACAGCGCTCGTGAGGAAGCTCATCCTACTGAAGCGAGAAGACTTATAACCA  
CCGCGTCTCCTCCTCCACCACCTCATCCCGCCCACCTGTGTGGGGCTGACCAATGCAAAC  
TCAAATGGTGTCTTCAAAGGGAGAGACCCACTGACTCTCCTTCCTTTACTCTTATGCCATT  
GGTCCCATCATTCTTGTGGGGGAAAAATTCTAGTATTTTGATTATTTGAATCTTACAGCA  
ACAAATAGGAACTCCTGGCCAATGAGAGCTCTTGACCAGTGAATCACCAGCCGATACGAA  
CGTCTTGCCAACAAAAATGTGTGGCAAATAGAAGTATATCAAGCAATAATCTCCACCCA  
AGGCTTCTGTAAACTGGGACCAATGATTACCTCATAGGGCTGTTGTGAGGATTAGGATGA  
AATACCTGTGAAAGTGCCTAGGCAGTGCCAGCCAAATAGGAGGCATTCAATGAACATTTT  
TTGCATATAAACCAAAAAATAACTTGTTATCAATAAAAACTTGCATCCAACATGAATTTCT  
CAGCCGATGATAATCCAGGCCAAAGGTTTAGTTGTTGTTATTTTCTGTATTATTTTCT  
TCATTACAAAAGAAATGCAAGTTCATTGTAACAATCCAAACAATACCTCACGATATAAAA  
TAAAAATGAAAGTATCCTCCTCAAAAA

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**FIGURE 124**

MVAATVAAAWLLLWAAACAQQEQDFYDFKAVNIRGKLVSLVKYRGSVSLVVNVASECGFT  
DQHYRALQQLQORDLGPHHFNVLAFFPCNQFGQQEPDSNKEIESFARRTYSVSFPMFSKIAV  
TGTGAHPAFKYLAQTSGKEPTWNFWKYLVA PDGKVVGAWDPTVSVEEVRPQITALVRKLI  
LLKREDL

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**FIGURE 125**

CGGACGCGTGGGCGGACGCGTGGGCGGACGCGTGGGTTGGGAGGGGGCAGGATGGGAGGG  
AAAGTGAAGAAAACAGAAAAGGAGAGGGACAGAGGCCAGAGGACTTCTCATACTGGACAG  
AAACCGATCAGGCATGGAACTCCCCCTTCGTCACTCACCTGTTCTTGCCCCCTGGTGTTCCCT  
GACAGGTCTCTGCTCCCCCTTTAACCTGGATGAACATCACCCACGCCTATTCCCAGGGCC  
ACCAGAAAGCTGAATTTGGATACAGTGTCTTACAACATGTTGGGGGTGGACAGCGATGGAT  
GCTGGTGGGCGCCCCCTGGGATGGGCCTTCAGGCGACCGGAGGGGGGACGTTTATCGCTG  
CCCTGTAGGGGGGGGCCACAATGCCCCATGTGCCAAGGGCCACTTAGGTGACTACCAACT  
GGGAAATTCATCTCATCCTGCTGTGAATATGCACCTGGGGATGTCTCTGTAGAGACAGA  
TGGTGATGGGGGATTTCATGGTGAGCTAAGGAGAGGGTGGTGGCAGTGTCTCTGAAGGTCC  
ATAAAAGAAAAAGAGAAGTGTGGTAAAGGAAAATGGTCTGTGTGGAGGGGTCAAGGAGT  
TAAAAACCCTAGAAAGCAAAAGGTAGGTAATGTCAGGGAGTAGTCTTCATGCCTCCTTCA  
ACTGGGAGCATGTTCTGAGGGTGCCCTCCCAAGCCTGGGAGTAATAATTTCCCCCATCCC  
CAGGCCTGTGCCCCCTCTCTGGTCTCGTGCTTGTGGCAGCTCTGTCTTCAGTTCTGGGATA  
TGTGCCCCGTGTGGATGCTTCATTCCAGCCTCAGGGAAGCCTGGCACCCACTGCCAACGT  
GAGCCAGAGGAAGGCTGAGTACTTGGTTCCAGAAGGAGATACTGGGTGGGAAAAAGATG  
GGGCAAAGCGGTATGATGCCTGGCAAAGGGCCTGCATGGCTATCCTCATTGCTACCTAAT  
GTGCTTGCAAAGCTCCATGTTTCCTAACAGATTTCAGACTCCTGGCCAGGTGTGGTGGCC  
CACACCTGTAATTCTAGCACTTTGGGAGGCCAAGGTGGGCAGATCACTTGAGGTCAGGAG  
TTCAAGACCAGCCTGGCCAACATGGTGAACTCCATCTCTACTAAAAAATAATAACA  
AAAATTAGCTGGGTGCGCTAGTGCATGCCTGTAATCTCATCTACTCGGGAGGCTAAGACA  
GGAGACTCTCACTTCAACCCAGGAGGTGGAGGTTGCGGTGAGCCAAGATTGTGCCTCTGC  
ACTCTAGCGTGGGTGACAGAGTAAGCGAGACTCCATCTCAAAAATAATAATAATAAT  
TCAGACTCCTTATCAGGAGTCCATGATCTGGCCTGGCACAGTAACTCATGCCTGTAATCC  
CAACATTTTGGGAGGCCAACGCAGGAGGATTGCTTGAGGTCTGGAGGTTTGAGACCAGCC  
TGGGCAACATAGAAAGACCCCATCTCTAAATAAATGTTTAAAAAT

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**FIGURE 126**

MELPFVTHLFLPLVFLTGLCSPFNLDEHHPRLFPGPPEAEFGYSVLQHVGGGQRWMLVGA  
PWDGPSGDRRGDVYRCPVGGAHNAPCAKGHLGDYQLGNSSHPAVNMHLGMSLLETGDG  
FMVS

**Important features:**

**Signal peptide:**

amino acids 1-22

**Cell attachment sequence:**

amino acids 70-73

**N-glycosylation site:**

amino acids 98-101

**Integrins alpha chain proteins:**

amino acids 67-81

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**FIGURE 127**

GAGAGGACGAGGTGCCGCTGCCTGGAGAATCCTCCGCTGCCGTCGGCTCCCGGAGCCCAG  
CCCTTTCCTAACCCAACCAACCTAGCCCAGTCCCAGCCGCCAGCGCCTGTCCCTGTAC  
GGACCCCAGCGTTACCAATGCATCCTGCCGTCTTCCTATCCTTACCCGACCTCAGATGCTC  
CCTTCTGCTCCTGGTAACTTGGGTTTTTACTCCTGTAACAACCTGAAATAACAAGTCTTGC  
TACAGAGAATATAGATGAAATTTTAAACAATGCTGATGTTGCTTTAGTAAATTTTATGC  
TGACTGGTGTTCGTTTCAGTCAGATGTTGCATCCAATTTTGTAGGAAGCTTCCGATGTCAT  
TAAGGAAGAATTTCCAAATGAAAATCAAGTAGTGTGTTGCCAGAGTTGATTGTGATCAGCA  
CTCTGACATAGCCCAGAGATAACAGGATAAGCAAATACCCAACCCCTCAAATTGTTTCGTAA  
TGGGATGATGATGAAGAGAGAATACAGGGGTCAGCGATCAGTGAAAGCATTGGCAGATTA  
CATCAGGCAACAAAAAAGTGACCCCATTCAGAAATTCGGGACTTAGCAGAAATCACCAC  
TCTTGATCGCAGCAAAAGAAATATCATTGGATATTTTGAGCAAAAGGACTCGGACAACCTA  
TAGAGTTTTTGAACGAGTAGCGAATATTTTGCATGATGACTGTGCCTTTCTTTCTGCATT  
TGGGGATGTTTCAAACCGGAAAGATATAGTGCGACAACATAATCTACAAACCACCAGG  
GCATTCTGCTCCGGATATGGTGTACTTGGGAGCTATGACAAATTTTGATGTGACTTACAA  
TTGGATTCAAGATAAATGTGTTCTCTTGTCCGAGAAATAACATTTGAAAATGGAGAGGA  
ATTGACAGAAGAAGGACTGCCTTTTCTCATACTCTTTCACATGAAAGAAGATACAGAAAG  
TTTAGAAATATTCCAGAATGAAGTAGCTCGGCAATTAATAAGTGAAAAAGGTACAATAAA  
CTTTTTACATGCCGATTGTGACAAATTTAGACATCCTCTTCTGCACATACAGAAAACCTCC  
AGCAGATTGTCTGTAATCGCTATTGACAGCTTTAGGCATATGTATGTGTTTGGAGACTT  
CAAAGATGTATTAATTCCTGGAAAACTCAAGCAATTCGTATTTGACTTACATTCTGGAAA  
ACTGCACAGAGAATTCCATCATGGACCTGACCCAACTGATACAGCCCCAGGAGAGCAAGC  
CCAAGATGTAGCAAGCAGTCCACCTGAGAGCTCCTTCCAGAACTAGCACCCAGTGAATA  
TAGGTATACTCTATTGAGGGATCGAGATGAGCTTTTAAAAACTTGAAAAACAGTTTGTAAG  
CCTTTCAACAGCAGCATCAACCTACGTGGTGGAATAGTAAACCTATATTTTTCATAATTC  
TATGTGTATTTTTTATTTTGAATAAACAGAAAGAAATTTAAAAA  
AAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAA

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**FIGURE 128**

MHPAVFLSLPDLRCSLLLLVTWVFTPVTTEITSLATENIDEILNNADVALVNFYADWCRF  
SQMLHPIFEEASDVIKEEFPNENQVVFARVDCDQHSDIAQRYRISKYPTLKLFRNGMMMK  
REYRGQRSVKALADYIRQQKSDPIQEIRDLAEITTLDRSKRNIIGYFEQKDSDNRYRVFER  
VANILHDDCAFLSAFGDVSKPERYSGDNIIYKPPGHSAPDMVYLGAMTNFDVTYNWIQDK  
CVPLVREITFENGEEELTEEGLPFLILFHMKEDTESLEIFQNEVARQLISEKGTINFLHAD  
CDKFRHPLLHIQKTPADCPVIAIDSFRHMYVFGDFKDVLIPGKLKQFVFDLHSGKLHREF  
HHGPDPTDTAPGEQAQDVASSPPESSFQKLAPSEYRYTLLRDRDEL

**Important features:**

**Signal peptide:**

amino acids 1-29

**Endoplasmic reticulum targeting sequence:**

amino acids 403-406

**Tyrosine kinase phosphorylation site:**

amino acids 203-211

**Thioredoxin family proteins:**

amino acids 50-66

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**FIGURE 129**

GAGCAGGACGGAGCCATGGACCCCGCCAGGAAAGCAGGTGCCCAGGCCATGATCTGGACT  
GCAGGCTGGCTGCTGCTGCTGCTGCTTTCGCGGAGGAGCGCAGGCCCTGGAGTGCTACAGC  
TGCGTGAGAAAGCAGATGACGGATGCTCCCCGAACAAGATGAAGACAGTGAAGTGCGCG  
CCGGGCGTGGACGTCTGCACCGAGGCCGTGGGGGCGGTGGAGACCATCCACGGACAATTC  
TCGCTGGCAGTGCGGGGTTGCGGTTGCGGACTCCCCGGCAAGAATGACCGCGGCCTGGAT  
CTTCACGGGCTTCTGGCGTTCATCCAGCTGCAGCAATGCGCTCAGGATCGCTGCAACGCC  
AAGCTCAACCTCACCTCGCGGGCGCTCGACCCGGCAGGTAATGAGAGTGATACCCGCCC  
AACGGCGTGGAGTGCTACAGCTGTGTGGGCCTGAGCCGGGAGGCGTGCCAGGGTACATCG  
CCGCCGGTCTGAGCTGCTACAACGCCAGCGATCATGTCTACAAGGGCTGCTTCGACGGC  
AACGTCACCTTGACGGCAGCTAATGTGACTGTGTCTTGCCTGTCCGGGGCTGTGTCCAG  
GATGAATTCTGCACTCGGGATGGAGTAACAGGCCAGGGTTCACGCTCAGTGGCTCCTGT  
TGCCAGGGGTCCCGCTGTAACCTTGACCTCCGCAACAAGACCTACTTCTCCCCTCGAATC  
CCACCCCTTGTCGGGCTGCCCCCTCCAGAGCCACGACTGTGGCCTCAACCACATCTGTC  
ACCACTTCTACCTCGGCCCCAGTGAGACCCACATCCACCACCAAACCCATGCCAGCGCCA  
ACCAGTCAGACTCCGAGACAGGGAGTAGAACACGAGGCCCTCCGGGATGAGGAGCCAGG  
TTGACTGGAGGCGCCGCTGGCCACCAGGACCGCAGCAATTCAGGGCAGTATCCTGCAAAA  
GGGGGGCCCCAGCAGCCCCATAATAAAGGCTGTGTGGCTCCACAGCTGGATTGGCAGCC  
CTTCTGTTGGCCGTGGCTGCTGGTGTCTTACTGTGAGCTTCTCCACCTGGAAATTTCCCT  
CTCACCTACTTCTCTGGCCCTGGGTACCCCTCTTCTCATCACTTCCTGTTCCCACTG  
GACTGGGCTGGCCAGCCCCCTGTTTTTCCAACATTCCCCAGTATCCCAGCTTCTGCTGC  
GCTGGTTTGCGGCTTTGGGAAATAAAATACCGTTGTATATATTCTGCCAGGGGTGTTCTA  
GCTTTTTGAGGACAGCTCCTGTATCCTTCTCATCCTTGTCTCTCCGCTTGTCCTCTGTG  
ATGTTAGGACAGAGTGAGAGAAGTCAGCTGTCACGGGGAAGGTGAGAGAGAGGATGCTAA  
GCTTCCTACTCACTTTCTCCTAGCCAGCCTGGACTTTGGAGCGTGGGGTGGGTGGGACAA  
TGGCTCCCCACTCTAAGCACTGCCTCCCCTACTCCCCGCATCTTTGGGGAATCGGTTCCC  
CATATGTCTTCTTACTAGACTGTGAGCTCCTCGAGGGGGGGCCCGGTACCCAATTGCCC  
CTATAGTGAGTCGTA



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**FIGURE 130**

MDPARKAGAQAMIWTAGWLLLLLLLRGGAQALECYSCVQKADDGCSPNKMKTVKCAPGVDV  
CTEAVGAVETIHGQFSLAVRGCGSLPGKNDRGLDLHGLLAFIQLQQCAQDRCNALNLT  
SRALDPAGNESAYPPNGVECYSCVGLSREACQGTSPFVVCYNASDHVYKGCDFGNVTLT  
AANVTVSLPVVRCVQDEFCTRDGVTGPGFTLSGSCCQGSRCNSDLRNKTYFSPRIPLVR  
LPPPEPTTVASTTSVTTSTAPVRPTSTTKPMPAPTSQTPRQVEHEASRDEEPRLTGGA  
AGHQDRSNSGQYPAKGGPQQPHNKGCVAPTAGLAALLLAVAAGVLL

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**FIGURE 131**

AAACTTGACGCCATGAAGATCCCGGTCCTTCCTGCCGTGGTGCTCCTCTCCCTCCTGGTG  
CTCCACTCTGCCCAGGGAGCCACCCTGGGTGGTCCTGAGGAAGAAAGCACCATTGAGAAT  
TATGCGTCACGACCCGAGGCCTTTAACACCCCGTTCCTGAACATCGACAAATTGCGATCT  
GCGTTTAAGGCTGATGAGTTCCTGAACTGGCACGCCCTCTTTGAGTCTATCAAAAGGAAA  
CTTCCTTTCCTCAACTGGGATGCCTTTCCTAAGCTGAAAGGACTGAGGAGCGCAACTCCT  
GATGCCCAGTGAACCATGACCTCCACTGGAAGAGGGGGCTAGCGTGAGCGCTGATTCTCAA  
CCTACCATAACTCTTTCCTGCCTCAGGAACTCCAATAAAACATTTTCCATCCAAA

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## FIGURE 132

MKIPVLPVAVLLSLLVLHSAQGATLGGPEEESTIENYASRPEAFNTPFLNIDKLRSAFKA  
DEFLNWHALFESIKRKLPFLNWDAFPKLKGLRSATPDAQ

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**FIGURE 133**

CAGTTCCTGAAATCAATGGAGTTAATTTAGGGAATACAAACCAGCCATGGGGGTGGAGATT  
GCCTTTGCCTCAGTGATTCTCACCTGCCTCTCCCTTCTGGCAGCAGGAGTCTCCAGGTT  
GTTCTTCTCCAGCCAGTTCCAACCTCAGGAGACAGGTCCCAAGGCCATGGGAGATCTCTCC  
TGTGGCTTTGCCGGCCACTCATGAGAGTGTTTTTGTGTAAAGTATTTTTTAGAATACTGT  
TGACTTCTTCATGATTTAATAACCATCCTTTGCGAAGTTTTATGAGGCTTTAGGGGAATG  
TCAACCCTCAAATTTTTGTTATACTAGATGGCTTCCATTTACCCACCACTATTTTAAGGT  
CCCTTTATTTTTAGGTTCAAGGTTCAATTTGACTTGAGAAAGTGCCCTTCTGCAGCTTCAT  
TGATTTTTGTTTATCTTCACTATTAATTGTAACGATTAAAAAAGAATAAGAGCACGCAGAC  
CTCTAGGAGAATATTTTTATCCCTGGGTGCCCCCTGACACATTTATGTAGTGATCCCAAAA  
TGTGATTGTTAATTTAAATGTTATTCTAATATTAGTACATTCAGTTGTGATGTAATATGA  
ATAACCAGAATCTATTTCTTAAAAGTTTTGAGTATATTTTTTCACTAGATATTTGTATAG  
AAAGACTGAATAGTGATG

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## FIGURE 134

MGVEIAFASVILTCLSLAAGVSQVLLQFVPTQETGPKAMGDLSCGFAGHS

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**FIGURE 135**

GGGGAATCTGCAGTAGGTCTGCCGGCGATGGAGTGGTGGGCTAGCTCGCCGCTTCGGCTC  
TGGCTGCTGTTGTTCCCTCCTGCCCTCAGCGCAGGGCCGCCAGAAGGAGTCAGGTTCAAAA  
TGGAAAGTATTTATTGACCAATTAACAGGTCTTTGGAGAATTACGAACCATGTTCAAGT  
CAAACTGCAGCTGCTACCATGGTGT CATAGAAGAGGATCTAACTCCTTTCCGAGGAGGC  
ATCTCCAGGAAGATGATGGCAGAGGTAGTCAGACGGAAGCTAGGGACCCACTATCAGATC  
ACTAAGAACAGACTGTACCGGGAAAATGACTGCATGTTCCCCTCAAGGTGTAGTGGTGTT  
GAGCACTTTATTTTGGAAAGTGATCGGGCGTCTCCCTGACATGGAGATGGTGATCAATGTA  
CGAGATTATCCTCAGGTTCCCTAAATGGATGGAGCCTGCCATCCCAGTCTTCTCCTTCAGT  
AAGACATCAGAGTACCATGATATCATGTATCCTGCTTGGACATTTTGGGAAGGGGGACCT  
GCTGTTTGGCCAATTTATCCTACAGGTCTTGGACGGTGGGACCTCTTCAGAGAAGATCTG  
GTAAGGTGAGCAGCACAGTGGCCATGGAAAAAGAAAACTCTACAGCATATTTCCGAGGA  
TCAAGGACAAGTCCAGAACGAGATCCTCTCATTTCTTCTGTCTCGGAAAAACCCAAAACTT  
GTTGATGCAGAATACACCAAAAACCAGGCCTGGAAATCTATGAAAGATACCTTAGGAAAG  
CCAGCTGCTAAGGATGTCCATCTTGTGGATCACTGCAAATACAAGTATCTGTTTAATTTT  
CGAGGCGTAGCTGCAAGTTTCCGGTTTAAACACCTCTTCTGTGTGGCTCACTTGTTTTTC  
CATGTTGGTGATGAGTGGCTAGAATTCTTCTATCCACAGCTGAAGCCATGGGTTCATAT  
ATCCCAGTCAAAACAGATCTCTCCAATGTCCAAGAGCTGTTACAATTTGTAAAAGCAAAT  
GATGATGTAGCTCAAGAGATTGCTGAAAGGGGAAGCCAGTTTATTAGGAACCATTTGCAG  
ATGGATGACATCACCTGTTACTGGGAGAACCTCTTGAGTGAATACTCTAAATTCCTGTCT  
TATAATGTAACGAGAAGGAAAGGTTATGATCAAATTATTCCCAAAATGTTGAAAACCTGAA  
CTATAGTAGTCATCATAGGACCATAGTCCTCTTTGTGGCAACAGATCTCAGATATCCTAC  
GGTGAGAAGCTTACCATAAGCTTGGCTCCTATACCTTGAATATCTGCTATCAAGCCAAAT  
ACCTGGTTTTTCCTTATCATGCTGCACCCAGAGCAACTCTTGAGAAAGATTTAAAATGTGT  
CTAATACACTGATATGAAGCAGTTCAACTTTTTTGGATGAATAAGGACCAGAAATCGTGAG  
ATGTGGATTTTTGAACCCAACTCTACCTTTTCATTTTCTTAAGACCAATCACAGCTTGTGCC  
TCAGATCATCCACCTGTGTGAGTCCATCACTGTGAAATTGACTGTGTCCATGTGATGATG  
CCCTTTGTCCCATTTATTTGGAGCAGAAAATTCGTCAATTTGGAAGTAGTACAACCTATTGC  
TGGAATTGTGAAATTATTCAAGGCGTGATCTCTGTCACTTTATTTTAAATGTAGGAAACCC  
TATGGGGTTTATGAAAAATACTTGGGGATCATTCTCTGAATGGTCTAAGGAAGCGGTAGC  
CATGCCATGCAATGATGTAGGAGTTCTCTTTTGTAAAACCATAAACTCTGTTACTCAGGA  
GGTTTCTATAATGCCACATAGAAAGAGGCCAATTGCATGAGTAATTATTGCAATTGGATT  
TCAGGTTCCCTTTTTTGTGCCTTCATGCCCTACTTCTTAATGCCTCTCTAAAGCCAAA

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**FIGURE 136**

MEWWASSPLRLWLLLFLLPSAQGRQKESGSKWKVFIDQINRSLENYEPCSSQNCSCYHGV  
IEEDLTPFRGGISRKMAEVVRRKLGTHYQITKNRLYREND CMFP SRCSGVEHFILEVIG  
RLPD MEMVINVRDYPQVPKWMEPAIPVFSFSKTSEYHDIMYPAWTFWEGGPAVWP IYPTG  
LGRWDLFREDLVRSAAQWPWKKNSTAYFRGSRTSPERDPLILLSRKNP KLVD AEYTKNQ  
AWKSMKDTLGKPAAKDVHLVDHCKYKYLNFNFRGVAASFRFKHLFLCGSLVFHVGDEWLEF  
FYPQLKPWVHYIPVKTDLSNVQELLQFVKANDDVAQEIAERGSQFIRNHLQMD DITCYWE  
NLLSEYSKFLSYNVTRRKG YDQIIPKMLKTEL

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**FIGURE 137**

ATTCTCCTAGAGCATCTTTGGAAGCATGAGGCCACGATGCTGCATCTTGGCTCTTGTCTG  
CTGGATAACAGTCTTCCTCCTCCAGTGTTCAAAGGAACTACAGACGCTCCTGTTGGCTC  
AGGACTGTGGCTGTGCCAGCCGACACCCAGGTGTGGGAACAAGATCTACAACCCTTCAGA  
GCAGTGCTGTTATGATGATGCCATCTTATCCTTAAAGGAGACCCGCCGCTGTGGCTCCAC  
CTGCACCTTCTGGCCCTGCTTTGAGCTCTGCTGTCCCGAGTCTTTTGGCCCCCAGCAGAA  
GTTTCTTGTGAAGTTGAGGGTTCTGGGTATGAAGTCTCAGTGTCACCTTATCTCCCATCTC  
CCGGAGCTGTACCAGGAACAGGAGGCACGTCCTGTACCCATAAAAAACCCAGGCTCCACT  
GGCAGACGGCAGACAAGGGGAGAAGAGACGAAGCAGCTGGACATCGGAGACTACAGTTGA  
ACTTCGGAGAGAAGCAACTTGACTTCAGAGGGATGGCTCAATGACATAGCTTTGGAGAGG  
AGCCCAGCTGGGGATGGCCAGACTTCAGGGGAAGAATGCCTTCCTGCTTCATCCCCTTTC  
CAGCTCCCCCTTCCCCTGAGAGCCACTTTCATCGGCAATAAAATCCCCACATTTACCATCT



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**FIGURE 138**

MRPRCCILALVCWITVFLQCSKGTTDAPVGSGLWLCQPTPRCGNKIYNPSEQCCYDDAI  
LSLKETRRCGSTCTFWPCFELCCPESFGPQQKFLVKLRVLGMKSQCHLSPIRSCTRNR  
HVLYP

**Important features:**

**Signal sequence:**

amino acids 1-21

**N-myristoylation sites:**

amino acids 33-39, 70-76

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**FIGURE 139**

CCTCTGTCCACTGCTTTTCGTGAAGACAAGATGAAGTTCACAATTGTCTTTGCTGGACTTC  
TTGGAGTCTTTCTAGCTCCTGCCCTAGCTAACTATAATATCAACGTCAATGATGACAACA  
ACAATGCTGGAAGTGGGCAGCAGTCAGTGAGTGTCAACAATGAACACAATGTGGCCAATG  
TTGACAATAACAACGGATGGGACTCCTGGAATTCATCTGGGATTATGGAAATGGCTTTG  
CTGCAACCAGACTCTTTCAAAGAAGACATGCATTGTGCACAAAATGAACAAGGAAGTCA  
TGCCCTCCATTCAATCCCTTGATGCACTGGTCAAGGAAAAGAAGCTTCAGGGTAAGGGAC  
CAGGAGGACCACCTCCCAAGGGCCTGATGTACTCAGTCAACCCAAACAAAGTCGATGACC  
TGAGCAAGTTCGGAAAAAACATTGCAAACATGTGTCTGCGGGATTCCAACATACATGGCTG  
AGGAGATGCAAGAGGCAAGCCTGTTTTTTTACTCAGGAACGTGCTACACGACCAGTGTAC  
TATGGATTGTGGACATTTCTTTCTGTGGAGACACGGTGGAGAACTAAACAATTTTTTAAA  
GCCACTATGGATTTAGTCATCTGAATATGCTGTGCAGAAAAAATATGGGCTCCAGTGGTT  
TTTACCATGTCAATCTGAAATTTTTCTCTACTAGTTATGTTTGATTTCTTTAAGTTTCAA  
TAAATCATTTAGCATTGAAAAAA

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**FIGURE 140**

MKFTIVFAGLLGVFLAPALANYNINVNDDNNNAGSGQQSVSVNNEHNVANVDNNGWDSW  
NSIWDYGNNGFAATRLFQKKTCIVHKMNKEVMPSIQSLDALVKEKKLQKGPGGPPPKGLM  
YSVNPKNKVDLDSKFGKNIANMCRGIPTYMAEEMQEASLFFYSGTCYTTSVLWIVDISFCG  
DTVEN

**Signal Peptide:**  
amino acids 1-20

**N-myristoylation Sites:**  
amino acids 67-72, 118-123, 163-168

**Flavodoxin protein homology:**  
amino acids 156-174

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**FIGURE 141**

GGTCCTTAATGGCAGCAGCCGCCGCTACCAAGATCCTTCTGTGCCTCCCGCTTCTGCTCC  
TGCTGTCCGGCTGGTCCCGGGCTGGGCGAGCCGACCCTCACTCTCTTTGCTATGACATCA  
CCGTCATCCCTAAGTTTCAAGACCTGGACCACGGTGGTGTGCGGTTCAAGGCCAGGTGGATG  
AAAAGACTTTTCTTCACTATGACTGTGGCAACAAGACAGTCACACCTGTCAGTCCCCTGG  
GGAAGAACTAAATGTCACAACGGCCTGGAAAGCACAGAACCCAGTACTGAGAGAGGTGG  
TGGACATACTTACAGAGCAACTGCGTGACATTGAGCTGGAGAATTACACACCCAAGGAAC  
CCCTCACCTGTCAGGCAAGGATGTCTTGTGAGCAGAAAGCTGAAGGACACAGCAGTGGAT  
CTTGGCAGTTCAGTTTCGATGGGCAGATCTTCCTCCTCTTTGACTCAGAGAAGAGAATGT  
GGACAACGGTTCATCCTGGAGCCAGAAAGATGAAAGAAAAGTGGGAGAATGACAAGGTG  
TGGCCATGTCCTTCCATTACTTCTCAATGGGAGACTGTATAGGATGGCTTGAGGACTTCT  
TGATGGGCATGGACAGCACCTGGAGCCAAGTGCAGGAGCACCCTCGCCATGTCCTCAG  
GCACAACCCAACCTCAGGGCCACAGCCACCACCCTCATCCTTTGCTGCCTCCTCATCATCC  
TCCCCTGCTTCATCCTCCCTGGCATCTGAGGAGAGTCCTTTAGAGTGACAGGTTAAAGCT  
GATACCAAAGGCTCCTGTGAGCACGGTCTTGATCAAACCTCGCCCTTCTGTCTGGCCAGC  
TGCCCACGACCTACGGTGTATGTCCAGTGGCCTCCAGCAGATCATGATGACATCATGGAC  
CCAATAGCTCATTCATGCTTGCCTTGATTCTTTTGCCAACAATTTTACCAGCAGTTATACCT  
AACATATTATGCAATTTTCTCTTGGTGCTACCTGATGGAATTCCTGCACTTAAAGTTCTG  
GCTGACTAAACAAGATATATCATTTTTCTTTCTTCTTTTTGTTTGGAAAATCAAGTACT  
TCTTTGAATGATGATCTCTTTCTTGCAAATGATATTGTCAGTAAAATAATCACGTTAGAC  
TTCAGACCTCTGGGGATTCTTTCCGTGTCCTGAAAGAGAATTTTTAAATTATTTAATAAG  
AAAAAATTTATATTAATGATTGTTTCCTTTAGTAATTTATTGTTCTGTACTGATATTTAA  
ATAAAGAGTTCTATTTCCCAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 142**

MAAAAATKILLCLPLLLLLSGWSRAGRADPHSLCYDITVIPKFRPGPRWCAVQGQVDEKT  
FLHYDCGNKTVTPVSPILGKKLNVTTAWKAQNPVLREVVDILTEQLRDIQLENYTPKEPLT  
LQARMSCEQKAEGHSSGSWQFSFDGQIFLLFDSEKRMWTTVHPGARKMKEKWENDKVVAM  
SFHYFSMGDCIGWLEDFLMGMDSTLEPSAGAPLAMSSGTTQLRATATTLILCCLLIILPC  
FILPGI

**Important features:****Signal peptide:**

amino acids 1-25

**Transmembrane domain:**

amino acids 224-246

**N-glycosylation site:**

amino acids 68-72, 82-86

**N-myristoylation site:**

amino acids 200-206, 210-216

**Amidation site:**

amino acids 77-81

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**FIGURE 143**

AATGTGAGAGGGGCTGATGGAAGCTGATAGGCAGGACTGGAGTGTTAGCACCAGTACTGG  
ATGTGACAGCAGGCAGAGGAGCACTTAGCAGCTTATTCAGTGTCCGATTCTGATTCCGGC  
AAGGATCCAAGCATGGAATGCTGCCGTCGGGCAACTCCTGGCACACTGCTCCTCTTTCTG  
GCTTTCTGCTCCTGAGTTCCAGGACCGCACGCTCCGAGGAGGACCGGGACGGCCTATGG  
GATGCCTGGGGCCCATGGAGTGAATGCTCACGCACCTGCGGGGGAGGGGCTCCTACTCT  
CTGAGGCGCTGCCTGAGCAGCAAGAGCTGTGAAGGAAGAAATATCCGATACAGAACATGC  
AGTAATGTGGACTGCCACCAGAAGCAGGTGATTTCCGAGCTCAGCAATGCTCAGCTCAT  
AATGATGTCAAGCACCATGGCCAGTTTTATGAATGGCTTCCTGTGTCTAATGACCCTGAC  
AACCCATGTTCACTCAAGTGCCAAGCCAAAGGAACAACCCTGGTTGTTGAACTAGCACCT  
AAGGTCTTAGATGGTACGCGTTGCTATACAGAATCTTTGGATATGTGCATCAGTGGTTTA  
TGCCAAATTGTTGGCTGCGATCACCAGCTGGGAAGCACCGTCAAGGAAGATAACTGTGGG  
GTCTGCAACGGAGATGGGTCCACCTGCCGGCTGGTCCGAGGGCAGTATAAATCCCAGCTC  
TCCGCAACCAAATCGGATGATACTGTGGTTGCACTTCCCTATGGAAGTAGACATATTCGC  
CTTGTCTTAAAGGTCTGATCACTTATATCTGGAAACCAAACCCTCCAGGGGACTAAA  
GGTGAAAACAGTCTCAGCTCCACAGGAACTTTCTTGTGGACAATTCTAGTGTGGACTTC  
CAGAAATTTCCAGACAAAGAGATACTGAGAATGGCTGGACCACTCACAGCAGATTTTATT  
GTCAAGATTTCGTAACTCGGGCTCCGCTGACAGTACAGTCCAGTTCATCTTCTATCAACCC  
ATCATCCACCGATGGAGGGAGACGGATTTCTTTCTTGCTCAGCAACCTGTGGAGGAGGT  
TATCAGCTGACATCGGCTGAGTGCTACGATCTGAGGAGCAACCGTGTGGTTGCTGACCAA  
TACTGTCACTATTACCCAGAGAACATCAAACCCAAACCCAAGCTTCAGGAGTGCAACTTG  
GATCCTTGTCCAGCCAGTGACGGATACAAGCAGATCATGCCTTATGACCTCTACCATCCC  
CTTCCTCGGTGGGAGGCCACCCCATGGACCGCGTGCTCCTCCTCGTGTGGGGGGGGCATC  
CAGAGCCGGGCAGTTTCTGTGTGGAGGAGGACATCCAGGGGCATGTCACTTCAGTGGA  
GAGTGGAATGCATGTACACCCCTAAGATGCCCATCGCGCAGCCCTGCAACATTTTTTGAC  
TGCCCTAAATGGCTGGCACAGGAGTGGTCTCCGTGCACAGTGACATGTGGCCAGGGCCTC  
AGATAACCGTGTGGTCTCTGCATCGACCATCGAGGAATGCACACAGGAGGCTGTAGCCCA  
AAAACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACTCCCTGCTATAAACCCAAA  
GAGAACTTCCAGTCGAGGCCAAGTTGCCATGGTTCAAACAAGCTCAAGAGCTAGAAGAA  
GGAGCTGCTGTGTGAGAGGAGCCCTCGTAAGTTGTAAAGCACAGACTGTTCTATATTG  
AACTGTTTTGTTTAAAGAAAGCAGTGTCTCACTGGTTGTAGCTTTTCATGGGTCTGAAC  
TAAGTGTAATCATCTCACCAAAGCTTTTTGGCTCTCAAATTAAAGATTGATTAGTTTTCAA  
AAAAAAAAA

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**FIGURE 144**

MECCRRATPGTLLLFLAFLLLSSRTARSEEDRDGLWDAWGPWSECSRTC GGGASYSLRRC  
LSSKSCEGRNIRYRTCSNVDCPPEAGDFRAQQCSAHNDVKHHGQFYEWLPVSNDPDNPCS  
LKCQAKGTTLVVELAPKVL DGT RCYTESLDMCISGLCQIVGCDHQLGSTVKEDNCGVCNG  
DGSTCRLVRGQYKSQLSATKSDDTVVALPYGSRHIRLV LKGP D HLYLETKTLQGTKGENS  
LSSTGTFLVDNSSVDFQKFPDKEILRMAGPLTAD FIVKIRNSGSADSTVQFIFYQPIIHR  
WRETDFFPCSATCGGGYQLTSAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCP  
ASDGYKQIMPYDLYHPLPRWEATPWTACSSSCGGGIQSRAVSCVEEDIQGHVTSVEEWKC  
MYTPKMPIAQPCNIFDCPKWLAQEWSPCTVT CGQGLRYRVVLCIDHRGMHTGGCSPKTKP  
HIKEECIVPTPCYKPKEKLPVEAKLPWFKQAQEEGA AVSEEPS

**Important features:****Signal peptide:**

amino acids 1-25

**N-glycosylation site:**

amino acids 251-254

**Thrombospondin 1:**

amino acids 385-399

**von Willebrand factor type C domain proteins:**

amino acids 385-399, 445-459 and 42-56

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**FIGURE 145**

GGAGGAGGGAGGGCGGGCAGGCGCCAGCCCAGAGCAGCCCCGGGCACCAGCACGGACTCT  
CTCTTCCAGCCCAGGTGCCCCCACTCTCGCTCCATTTCGGCGGGAGCACCCAGTCCTGTA  
CGCCAAGGAACTGGTCTCTGGGGGCACCAATGGTTTCGGCGGCAGCCCCCAGCCTCCTCATC  
CTTCTGTTGCTGCTGCTGGGGTCTGTGCCTGCTACCGACGCCCCGCTCTGTGCCCTGAAG  
GCCACGTTCTTGAGGATGTGGCGGGTAGTGGGGAGGCCGAGGGCTCGTCGGCCTCCTCC  
CCGAGCCTCCCGCCACCCTGGACCCCGGCCCTCAGCCCCACATCGATGGGGCCCCAGCCC  
ACAACCTTGGGGGGCCCATCACCCCCACCAACTTCTTGATGGGATAGTGGACTTCTTC  
CGCCAGTACGTGATGCTGATTGCTGTGGTGGGCTCCCTGGCCTTTCTGCTGATGTTTCATC  
GTCTGTGCCGCGGTTCATCACCCGGCAGAAGCAGAAGGCCTCGGCCTATTACCCATCGTCC  
TTCCCCAAGAAGAAGTACGTGGACCAGAGTGACCGGGCCGGGGCCCCCGGGCCTTCAGT  
GAGGTCCCCGACAGAGCCCCCGACAGCAGGCCCGAGGAAGCCCTGGATTCTCTCCCGGCAG  
CTCCAGGCCGACATCTTGCCCGCCACCCAGAACCTCAAGTCCCCACCAGGGCTGCACTG  
GGCGGTGGGGACGGAGCCAGGATGGTGGAGGGCAGGGGCGCAGAGGAAGAGGAGAAGGGC  
AGCCAGGAGGGGGACAGGAAGTCCAGGGACATGGGGTCCCAGTGGAGACACCAGAGGCG  
CAGGAGGAGCCGTGCTCAGGGGTCTTGAGGGGGCTGTGGTGGCCGGTGAGGGCCAAGGG  
GAGCTGGAAGGGTCTCTCTTGTTAGCCAGGAAGCCAGGGACCAGTGGGTCCCCCGAA  
AGCCCCCTGTGCTTGCAGCAGTGTCCACCCAGTGTCTAACAAGTCCTCCCGGGCTGCCAGC  
CCTGACTGTGCGGGCCCCCAAGTGGTCACCTCCCCGTGTATGAAAAGGCCTTCAGCCCTGA  
CTGCTTCTTGACACTCCCTCCTTGGCCTCCCTGTGGTGCCAATCCCAGCATGTGCTGATT  
CTACAGCAGGCAGAAATGCTGGTCCCCGGTGCCCCGGAGGAATCTTACCAAGTGCCATCA  
TCCTTCACCTCAGCAGCCCCAAAGGGCTACATCCTACAGCACAGCTCCCCTGACAAAGTG  
AGGGAGGGCACGTGTCCCTGTGACAGCCAGGATAAAACATCCCCCAAAGTGCTGGGATTA  
CAGGCGTGAGCCACCGTGCCCGGCCAAACTACTTTTAAAACAGCTACAGGGTAAATC  
CTGCAGCACCCACTCTGGAATACTGCTCTTAATTTTCTGAAGGTGGCCCCCTGTTTC  
TAGTTGGTCCAGGATTAGGGATGTGGGGTATAGGGCATTTAAATCCTCTCAAGCGCTCTC  
CAAGCACCCCCGGCCTGGGGGTGAGTTTCTCATCCCGCTACTGCTGCTGGGATCAGGTTG  
AATGAATGGAACCTTCTCTGTCTGGCCTCCAAAGCAGCCTAGAAGCTGAGGGGCTGTGTT  
TGAGGGGACCTCCACCTGGGGAAGTCCGAGGGGCTGGGGAAGGGTTTCTGACGCCCAGC  
CTGGAGCAGGGGGGCCCTGGCCACCCCTGTTGCTCACACATTGTCTGGCAGCCTGTGTC  
CACAATATTCTGTCAGTCCTCGACAGGGAGCCTGGGCTCCGTCTGCTTTAGGGAGGCTCT  
GGCAGGAGGTCTCTCCCCATCCCTCCATCTGGGGCTCCCCAACCTCTGCACAGCTCT  
CCAGGTGCTGAGATATAATGCACCAGCACATAAACCTTTATTCCGGCCTGAAAAAAAAA  
AAGA



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**FIGURE 146**

MVSAAAPSLILLLLLLLGSVPATDARSVPLKATFLEDVAGSGEAEAGSSASSPSLPPPWTP  
ALSPTSMGPQPTTLGGPSPPTNFLDGIVDFFRQYVMLIAVVGSLAFLLMFIVCAAVITRQ  
KQKASAYYPSSFPKKKYVDQSDRAGGPRAFSEVPDRAPDSRPEEALDSSRQLQADILAAT  
QNLKSPTRAALGGGDGARMVEGRGAEEEEKGSQEGDQEVQGHGVPVETPEAQEEPCSGVL  
EGAVVAGEGQGELEGSLLLAQEAQGPVGPPEPCACSSVHPSV

**Signal peptide:**  
amino acids 1-25

**Transmembrane domain:**  
amino acids 94-118

**N-myristoylation site:**  
amino acids 18-24, 40-46, 46-52, 145-151, 192-198, 193-199,  
211-217, 238-244, 242-248

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**FIGURE 147**

GAAAGACGTGGTCCTGACAGACAGACAATCCTATTCCCTACCAAATGAAGATGCTGCTG  
CTGCTGTGTTTGGGACTGACCCTAGTCTGTGTCCATGCAGAAGAAGCTAGTTCTACGGGA  
AGGAACTTTAATGTAGAAAAGATTAATGGGGAATGGCATACTATTATCCTGGCCTCTGAC  
AAAAGAGAAAAGATAGAAGAACATGGCAACTTTAGACTTTTTCTGGAGCAAATCCATGTC  
TTGGAGAATTCCCTAGTTCTTAAAGTCCATACTGTAAGAGATGAAGAGTGCTCCGAATTA  
TCTATGGTTGCTGACAAAACAGAAAAGGCTGGTGAATATTCTGTGACGTATGATGGATTCT  
AATACATTTACTATACCTAAGACAGACTATGATAACTTTCTTATGGCTCACCTCATTAACT  
GAAAAGGATGGGGAAACCTTCCAGCTGATGGGGCTCTATGGCCGAGAACCAGATTTGAGT  
TCAGACATCAAGGAAAGGTTTGCACTACTATGTGAGGAGCATGGAATCCTTAGAGAAAAT  
ATCATTGACCTATCCAATGCCAATCGCTGCCTCCAGGCCCGAGAATGAAGAATGGCCTGA  
GCCTCCAGTGTTGAGTGGACACTTCTCACCAGGACTCCACCATCATCCCTTCCTATCCAT  
ACAGCATCCCCAGTATAAATTCTGTGATCTGCATTCCATCCTGTCTCACTGAGAAGTCCA  
ATTCCAGTCTATCAACATGTTACCTAGGATACCTCATCAAGAATCAAAGACTTCTTTAAA  
TTTCTCTTTGATACACCCTTGACAATTTTTCATGAAATTATTCCTCTTCCTGTTCAATAA  
ATGATTACCCTTGCACTTAA

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**FIGURE 148**

MKMLLLLCLGLTLVCVHAEESSTGRNFNVEKINGEWHTIILASDKREKIEEHGNFRLFL  
EQIHVLENSLVLKVHTVRDEECSELSMVADKTEKAGEYSVTYDGFNTFTIPKTDYDNFLM  
AHLINEKDGETFQLMGLYGREPDLS DIKERFAQLCEEHGILRENIIDLSNANRCLQARE

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**FIGURE 149**

GTGGACTCTGAGAAGCCCAGGCAGTTGAGGACAGGAGAGAGAAGGCTGCAGACCCAGAGG  
GAGGGAGGACAGGGAGTCGGAAGGAGGAGGACAGAGGAGGGCACAGAGACGCAGAGCAAG  
GGCGGCAAGGAGGAGACCTTGGTGGGAGGAAGACACTCTGGAGAGAGAGGGGGCTGGGCA  
GAGATGAAGTTCCAGGGGCCCCCTGGCCTGCCTCCTGCTGGCCCTCTGCCTGGGCAGTGGG  
GAGGCTGGCCCCCTGCAGAGCGGAGAGGAAAGCACTGGGACAAATATTGGGGAGGCCCTT  
GGACATGGCCTGGGAGACGCCCTGAGCGAAGGGGTGGGAAAGGCCATTGGCAAAGAGGCC  
GGAGGGGCAGCTGGCTCTAAAGTCAGTGAGGCCCTTGGCCAAGGGACCAGAGAAGCAGTT  
GGCACTGGAGTCAGGCAGGTTCCAGGCTTTGGCGCAGCAGATGCTTTGGGCAACAGGGTC  
GGGGAAGCAGCCCATGCTCTGGGAAACACTGGGCACGAGATTGGCAGACAGGCAGAAGAT  
GTCATTCGACACGGAGCAGATGCTGTCCGCGGCTCCTGGCAGGGGGTGCCTGGCCACAGT  
GGTGCTTGGGAAACTTCTGGAGGCCATGGCATCTTTGGCTCTCAAGGTGGCCTTGGAGGC  
CAGGGCCAGGGCAATCCTGGAGGTCTGGGGACTCCGTGGGTCCACGGATACCCCGGAAAC  
TCAGCAGGCAGCTTTGGAATGAATCCTCAGGGAGCTCCCTGGGGTCAAGGAGGCAATGGA  
GGGCCACCAAACCTTTGGGACCAACACTCAGGGAGCTGTGGCCCAGCCTGGCTATGGTTCA  
GTGAGAGCCAGCAACCAGAATGAAGGGTGACGAATCCCCCACCATCTGGCTCAGGTGGA  
GGCTCCAGCAACTCTGGGGGAGGCAGCGGCTCACAGTCGGGCAGCAGTGGCAGTGGCAGC  
AATGGTGACAACAACAATGGCAGCAGCAGTGGTGGCAGCAGCAGTGGCAGCAGCAGTGGC  
AGCAGCAGTGGCGGCAGCAGTGGCGGCAGCAGTGGTGGCAGCAGTGGCAACAGTGGTGGC  
AGCAGAGGTGACAGCGGCAGTGAGTCCTCCTGGGGATCCAGCACCGGCTCCTCCTCCGGC  
AACCACGGTGGGAGCGGCGGAGGAAATGGACATAAACCCGGGTGTGAAAAGCCAGGGAAAT  
GAAGCCCGCGGGAGCGGGGAATCTGGGATTTCAGGGCTTCAGAGGACAGGGAGTTTCCAGC  
AACATGAGGGAAATAAGCAAGAGGGCAATCGCCTCCTTGGAGGCTCTCGAGACAAATTAT

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**FIGURE 150**

MKFQGPLACLLLLALCLGSGEAGPLQSGEESTGTNIGEALGHGLGDALSEGVGKAIGKEAG  
GAAGSKVSEALQGQTREAVGTGVRQVPGFGAADALGNRVGEAAHALGNTGHEIGRQAE DV  
IRHGADAVRGSWQGVPGHSGAWETSGHGHIFGSQGGLGGQQQGNPGGLGTPWVHGYPGNS  
AGSFGMNPQGAPWGQGGNGGPPNFGTNTQGAVAQPGYGSVRASNQNEGCTNPPPSGSGGG  
SSNSGGGSGSGSGSSGSGSNGDNNNGSSSGSSSGSSSGSSSGSSSGSGSSSGSGSSGSGS  
RGDSGSESSWGSSTGSSSGNHGSGGGNGHKPGCEKPGNEARGSGESGIQGFRGQGVSSN  
MREISKEGNRLLGSGDNYRGQSSSWGSGGGDAVGGVNTVNSETSPGMFNFDTFWKNFKS  
KLGFINWDAINKDORSSRIP

Signal peptide:

amino acids 1-21

N-glycosylation site:

amino acids 265-269

Glycosaminoglycan attachment site:

amino acids 235-239, 237-241, 244-248, 255-259, 324-328,  
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**Casein kinase II phosphorylation site:**

amino acids 26-30, 109-113, 259-263, 300-304, 304-308

N-myristoylation site:

amino acids 17-23, 32-38, 42-48, 50-56, 60-66, 61-67, 64-70,  
74-80, 90-96, 96-102, 130-136, 140-146, 149-155, 152-158,  
155-161, 159-165, 163-169, 178-184, 190-196, 194-200,  
199-205, 218-224, 236-242, 238-244, 239-245, 240-246,  
245-251, 246-252, 249-252, 253-259, 256-262, 266-272,  
270-276, 271-277, 275-281, 279-285, 283-289, 284-290,  
287-293, 288-294, 291-297, 292-298, 295-301, 298-304,  
305-311, 311-317, 315-321, 319-325, 322-328, 323-329,  
325-331, 343-349, 354-360, 356-362, 374-380, 381-387,  
383-389, 387-393, 389-395, 395-401

Cell attachment sequence:

amino acids 301-304

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**FIGURE 151**

CGGCCACAGCTGGCATGCTCTGCCTGATCGCCATCCTGCTGTATGTCCTCGTCCAGTACC  
TCGTGAACCCCGGGGTGCTCCGCACGGACCCAGATGTCAAGAATATGAACACGTGGCTG  
CTGTTCCCTCCCCCTGTTCCCGGTGCAGGTGCAGACCCTGATAGTCGTGATCATCGGGATG  
CTCGTGCTCCTGCTGGACTTTCTTGGCTTGGTGCACCTGGGCCAGCTGCTCATCTTCCAC  
ATCTACCTGAGTATGTCCCCCACCCTAAGCCCCCGATCCCCCAAGGCTGGGTGGTCAGA  
GCTGCTCATCTTACACCTCTACTTGAGTATGTCCCTAACCCTGAGCCCCCACGCCTGGG  
GCCAGAGTCTTTGTCCCCCGTGTGCGCATGTGTTCAAGGTGAGCCTCTCCAGAAAGTGAG  
ATCATGGACAAAAAGGGCAAATCACAGGAAGAAATTAAATCCATGAGGACCCAGCAGGCC  
CAGCAAGAAGCTGAACTCACGCCGAGACCTGCAGGAGTGGTGCCAGGTGCTTGAAGTAAC  
AAGTTTAAATGTTTCAAGACAATGGAATGGAATCTATTAGGCAAGAACAGGACATTATG  
AAATAAGGACAGGTGGACTTCCAAAAACACAAGTAGAAATTCTAACAAATGAAATATATTA  
CAGGCAGGTCACCCACTAACCAAAACAACCTGAAGCGAGAGCTGTGGTCTTGCTTGGTCTCA  
CAGTGGGCACAGCGGTAGGCGGTGAGTCATGTTGCTGAACGACGGAGGGTAAACTCCCCA  
GCCCCAAGAAAACCTGTGTTGGAAGTAACAACAACCTCCCTGCTCCTGGCACCAGCCGTT  
TTGGTCATGGTGGGCCAGCTGCAAAGCGTCTTCCATTCTCTGGGCAGTGGTGGCCCCGAG  
GCTGTGGCCTCTCAGGGGGTTTCTGTGGACACGGGCAGCAGAGTGTGTCCAGGCCAGCCC  
CCAAGAATGCCCTGCTCCTGACAGCTTGGCCAACCCCTGGTCAGGGCAGAGGGAGTTGGG  
TGGGTCAGGCTCTGGGCTCACCTCCATCTCCAGAGCATCCCCTGCCTGCAGTTGTGGCAA  
GAACGCCCAGCTCAGAAATGAACACACCCCCACCAAGAGCCTCCTTGTTTCATAACCACAGGT  
TACCCTACAAACCACTGTCCCCACACAACCTGGGGATGTTTTTAAACACACACCTCTAA  
CGCATATCTTACAGTCACTGTTGTCTTGCCTGAGGGTTGAATTTTTTTTAAATGAAAGTGC  
AATGAAAATCACTGGATTAAATCCTACGGACACAGAGCTGAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAA

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## FIGURE 152

MNTWLLFLPLFPVQVQTLIVVIIGMLVLLLDLGLVHLGQLLIFHIYLSMSPTLSPRSPQ  
GWVVRAAHLTPLLEYVPNPEPPTPGARVFVPRVRMCSGSASPRSEIMDKKGKSQEEIKSM  
RTQQAQQEAEELTPRPAGVVPGA

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**FIGURE 153**

AACTGGAAGGAAAGAAAGAAAGGTCAGCTTTGGCCCAGATGTGGTTACCCCTTGGTCTCC  
TGTCTTTATGTCCTTCTCCTCTTCCTATTCTGTCATCTCCCTCACTTAAGTCTCAGGCCT  
GTCAGCAGCTCCTGTGGACATTGCCATCCCCTCTGGTAGCCTTCAGAGCAAACAGGACAA  
CCTATGTTATGGATGTTTCCACCAACCAGGGTAGTGGCATGGAGCACCGTAACCATCTGT  
GCTTCTGTGATCTCTATGACAGAGCCACTTCTCCACCTCTGAAATGTTCCCTGCTCTGAA  
ATCTGGCATGAGATGGCACAGGTGACCACGCAGAAGCCACCAGAATCTTGCCTGCCCTAT  
TCCTCCTCCCAAGTCTGTTCTCTTATTGTCAACCTCAGCACAAACAGGCTGGCGCCAATGG  
CATTACAGAGAAAGCAATCTGTGTGGCTAGTGGGCAGATTACCATGCAAGCCCCAGGAGA  
AATGGAGGAGCTTTGTAGCCACCTCCCTGTGAGCCAGTATTAACATGTCCCCTTCCCCCT  
GCCCCGCCGTAGATTGAGGACATTGCCCCCTGTGTGCCACCAAACCAGGACTTCCCCCTT  
GGCTTGGCATCCCTGGCTCTCTCCTGGTACCCAGCAAGACGTCTGTTCCAGGGCAGTGTA  
GCATCTTTCAAGCTCCGTTACTATGGCGATGGCCATGATGTTACAATCCCCTTGCCTGA  
ATAATCAAGTGGAAGGGGAAGCAGAGGGAAATGGGGCCATGTGAATGCAGCTGCTCTGT  
TCTCCCTACCCTGAGGAAAAACCAAAGGGAAGCAACAGGAACTTCTGCAACTGGTTTTTA  
TCGGAAGATCATCCTGCCTGCAGATGCTGTTGAAGGGGCACAAGAAATGTAGCTGGAGA  
AGATTGATGAAAGTGCAGGTGTGTAAGGAAATAGAACAGTCTGCTGGGAGTCAGACCTGG  
AATTCTGATTCCAACTCTTTATTACTTTGGGAAGTCACTCAGCCTCCCCGTAGCCATCT  
CCAGGGTGACGGAACCCAGTGTATTACCTGCTGGAACCAAGGAACTAACAATGTAGGTT  
ACTAGTGAATACCCCAATGGTTTCTCCAATTATGCCCATGCCACCAAAACAATAAAACAA  
AATTCTCTAACACTGAAA



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## FIGURE 154

MWLPLGLLSLCLSPLPILSSPSLKSQACQQLLWTLPSPLVAFRANRTTYVMDVSTNQGS  
MEHRNHLCFCDLYDRATSPPLKCSLL



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## FIGURE 156

MAGIKALISLSFGGAIGLMFLMLGCALPIYNKYWPLFVLFFYILSPIPYCIARRLVDDTD  
AMSNACKELAIFLTGTGIVVSAFGLPIVFARAHLEWGACALVLTGNTVIFATILGFFLVF  
GSNDDFSQWQW

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**FIGURE 157**

GTTCCTCATAGTTGGCGTCTTCTAAAGGAAAAACACTAAAATGAGGAACTCAGCGGACCG  
GGAGCGACGCAGCTTGAGGGAAGCATCCCTAGCTGTTGGCGCAGAGGGGCGAGGCTGAAG  
CCGAGTGGCCCGAGGTGTCTGAGGGGCTGGGGCAAAGGTGAAAGAGTTTCAGAACAAGCT  
TCCTGGAACCCATGACCCATGAAGTCTTGTCGACATTTATACCGTCTGAGGGTAGCAGCT  
CGAAACTAGAAGAAGTGGAGTGTGTCAGGGACGGCAGTATCTCTTTGTGTGACCCTGGC  
GGCCTATGGGACGTTGGCTTCAGACCTTTGTGATACACCATGCTGCGTGGGACGATGACG  
GCGTGGAGAGGAATGAGGCCTGAGGTCACTGGCTTGCTCCTCCTAGCCACAGCAGGC  
TGCTTTGCTGACTTGAACGAGGTCCCTCAGGTACCGTCCAGCCTGCGTCCACCGTCCAG  
AAGCCCGGAGGCACCTGTGATCTTGGGCTGCGTGGTGGAACTCCAAGGATGAATGTAACC  
TGGCGCCTGAATGGAAGGAGCTGAATGGCTCGGATGATGCTCTGGGTGTCTCATCACC  
CACGGGACCCTCGTCATCACTGCCCTTAACAACCACACTGTGGGACGGTACCAGTGTGTG  
GCCCCGATGCCTGCGGGGGCTGTGGCCAGCGTGCCAGCCACTGTGACACTAGCCAATCTC  
CAGGACTTCAAGTTAGATGTGCAGCACGTGATTGAAGTGGATGAGGGAAACACAGCAGTC  
ATTGCCTGCCACCTGCCTGAGAGCCACCCCAAAGCCAGGTCCGGTACAGCGTCAAACAA  
GAGTGGCTGGAGGCCTCCAGAGGTAACCTGATCATGCCCTCAGGGAACCTCCAGATT  
GTGAATGCCAGCCAGGAGGACGAGGGCATGTACAAGTGTGCAGCCTACAACCCAGTGACC  
CAGGAAGTGAAAACCTCCGGCTCCAGCGACAGGCTACGTGTGCGCCGCTCCACCGCTGAG  
GCTGCCCCGCATCATCTACCCCCCAGAGGCCCAAACCATCATCGTCACCAAAGGCCAGAGT  
CTCATTCTGGAGTGTGTGGCCAGTGGAATCCACCCCCACGGGTACCTGGGCCAAGGAT  
GGGTCCAGTGTACCGGCTACAACAAGACGCGCTTCTGTGAGCAACCTCCTCATCGAC  
ACCACCAGCGAGGAGGACTCAGGCACCTACCGCTGCATGGCCGACAATGGGGTTGGGCAG  
CCCGGGGCAGCGGTATCCTCTACAATGTCCAGGTGTTTGAACCCCCTGAGGTACCATG  
GAGCTATCCCAGCTGGTCATCCCCTGGGGCCAGAGTGCCAAGCTTACCTGTGAGGTGCGT  
GGGAACCCCCCGCCCTCCGTGCTGTGGCTGAGGAATGCTGTGCCCTCATCTCCAGCCAG  
CGCCTCCGGCTCTCCCGCAGGGCCCTGCGCGTGCTCAGCATGGGGCCTGAGGACGAAGGC  
GTCTACCAGTGCATGGCCGAGAACGAGGTTGGGAGCGCCCATGCCGTAGTCCAGCTGCGG  
ACCTCCAGGCCAAGCATAACCCCAAGGCTATGGCAGGATGCTGAGCTGGCTACTGGCACA  
CCTCCTGTATCACCCCTCAAACCTCGGCAACCCCTGAGCAGATGCTGAGGGGGCAACCGGCG  
CTCCCCAGACCCCCAACGTCAGTGGGGCCTGCTTCCCCGAAGTGTCCAGGAGAGAAGGGG  
CAGGAGGCTCCCGCCGAGGCTCCCATCATCTCAGCTCGCCCCGCACCTCCAAGACAGAC  
TCATATGAACCTGGTGTGGCGGCTCGGCATGAGGGCAGTGGCCGGGCGCAATCCTCTAC  
TATGTGGTGAAACACCGCAAGCAGGTACAAATTCCTCTGACGATTGGACCATCTCTGGC  
ATTCCAGCCAACCAGCACCGCCTGACCCCTACCAGACTTGACCCCGGGAGCTTGTATGAA  
GTGGAGATGGCAGCTTACAACCTGTGCGGGAGAGGGCCAGACAGCCATGGTCACCTTCCGA  
ACTGGACGGCGGCCCAAACCCGAGATCATGGCCAGCAAAGAGCAGCAGATCCAGAGAGAC  
GACCCTGGAGCCAGTCCCCAGAGCAGCAGCCAGCCAGACCACGGCCGCTCTCCCCCCA  
GAAGCTCCCGACAGGCCACCATCTCCACGGCCTCCGAGACCTCAGTGACGTGACCTGG  
ATTCCCCGTGGGAATGGTGGGTTCCCAATCCAGTCCCTTCCGTGTGGAGTACAAGAAGCTA  
AAGAAAGTGGGAGACTGGATTCTGGCCACCAGCGCCATCCCCCATCGCGGCTGTCCGTG  
GAGATCACGGGCCTAGAGAAAGGCACCTCCTACAAGTTTCGAGTCCGGGCTCTGAACATG  
CTGGGGGAGAGCGAGCCAGCGCCCCCTCTCGGCCCTACGTGGTGTGCGGCTACAGCGGT  
CGCGTGTACGAGAGGCCCCGTGGCAGGTCTTATATCACCTTACGGATGCGGTCAATGAG  
ACCACCATCATGCTCAAGTGGATGTACATCCAGCAAGTAACAACAACACCCCAATCCAT  
GGCTTTTATATCTATTATCGACCCACAGACAGTGAACAATGATAGTGACTACAAGAAGGAT  
ATGGTGAAGGGGACAAGTACTGGCACTCCATCAGCCACCTGCAGCCAGAGACCTCCTAC  
GACATTAAGATGCAGTGCTTCAATGAAGGAGGGGAGAGCGAGTTCAGCAACGTGATGATC  
TGTGAGACCAAAGCTCGGAAGTCTTCTGGCCAGCCTGGTCGACTGCCACCCCCAACTCTG  
GCCCCACCACAGCCGCCCTTCTGAAACCATAGAGCGGCCGGTGGGCACTGGGGCCATG  
GTGGCTCGCTCCAGCGACCTGCCCTATCTGATTGTGCGGGTCTGCTGGGCTCCATCGTT  
CTCATCATCGTCACCTTCATCCCCTTCTGCTTGTGGAGGGCCTGGTCTAAGCAAAAACAT  
ACAACAGACCTGGGTTTTCTCGAAGTGCCCTTCCACCTCCTGCCCCGTATACTATGGTG  
CCATTGGGAGGACTCCAGGCCACCAGGCCAGTGGACAGCCCTACCTCAGTGGCATCAGT

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GGACGGGCCTGTGCTAATGGGATCCACATGAATAGGGGCTGCCCCTCGGCTGCAGTGGGC  
TACCCGGGCATGAAGCCCCAGCAGCACTGCCCAGGCGAGCTTCAGCAGCAGAGTGACACC  
AGCAGCCTGCTGAGGCAGACCCATCTTGGCAATGGATATGACCCCCAAAGTCACCAGATC  
ACGAGGGGTCCCAAGTCTAGCCCGGACGAGGGCTCTTTCTTATACACACTGCCCGACGAC  
TCCACTCACCAGCTGCTGCAGCCCCATCACGACTGCTGCCAACGCCAGGAGCAGCCTGCT  
GCTGTGGGCCAGTCAGGGGTGAGGAGAGCCCCGACAGTCCTGTCTGGAAGCAGTGTGG  
GACCTCCATTTCACTCAGGGCCCCCATGCTGCTTGGGCCTTGTGCCAGTTGAAGAGGTG  
GACAGTCCTGACTCCTGCCAAGTGAGTGGAGGAGACTGGTGTCCCCAGCACCCCGTAGGG  
GCCTACGTAGGACAGGAACCTGGAATGCAGCTCTCCCCGGGGGCCACTGGTGCGTGTGTCT  
TTTGAACACACCCTCTCACAATTTAGGCAGAAGCTGATATCCCAGAAAGACTATATATT  
GTTTTTTTTTTTAAAAAAAAGAAGAAAAAGAGACAGAGAAAATTGGTATTTATTTTTC  
TATTATAGCCATATTTATATATTTATGCACTTGTAATAAATGTATATGTTTTATAATTC  
TGGAGAGACATAAGGAGTCCTACCCGTTGAGGTTGGAGAGGGAAAATAAAGAAGCTGCCA  
CCTAACAGGAGTCACCCAGGAAAGCACCGCACAGGCTGGCGCGGGACAGACTCCTAACCT  
GGGGCCTCTGCAGTGGCAGGCGAGGCTGCAGGAGGCCACAGATAAGCTGGCAAGAGGAA  
GGATCCCAGGCACATGGTTCATCACGAGCATGAGGGAACAGCAAGGGGCACGGTATCACA  
GCCTGGAGACACCCACACAGATGGCTGGATCCGGTGCTACGGGAAACATTTTCCTAAGAT  
GCCCATGAGAACAGACCAAGATGTGTACAGCACTATGAGCATTAACCACTTCCAGAAT  
CAATAATCCGTGGCAACATATCTCTGTAAAAACAAACACTGTAACCTCTAAATAAATGTT  
TAGTCTTCCCTGTAAAA

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**FIGURE 158**

MLRGTMTAWRGMRPEVTLACLLLLATAGCFADLNEVPQVTVQPASTVQKPGGTIVILGCVVE  
PPRMNVTWRLNGKELNGSDDALGVLI THGTLVITALNNHTVGRYQCVARMPAGAVASVPA  
TVTLANLQDFKLDVQHVIEVDEGNTAVIACHLPESHKPAQVRYSVKQEWLEASRGNYLIM  
PSGNLQIVNASQEDEGMYKCAAYNPVTQEVKTS GSSDRLRVRRSTAEAAARI IYPPEAQTI  
IVTKGQSLILECVASGIPPPRVTWAKDGSSVTGYNKTRFLLSNLLIDTTSEEDSGTYRCM  
ADNGVGQPGA AVILYNVQVFEPPEVTMELS QLVI PWGQSAKLTCEVRGNPPPSVLWLRNA  
VPLISSQRLRLSRALRVLSMGPEDEGVYQCAENEVGS AHAVVQLRTSRPSITPRLWQD  
AELATGTPPVSPSKLGNPEQMLRGQPALPRPPTSVGPASPKCPGEKGQGAPAEAPIILSS  
PRTSKTDSYELVWRPRHEGSGRAPILYYVVKHRKQVTNSSDDWTISGIPANQHRLTLTRL  
DPGSLYEVEMAAYNCAGEGQTAMVTFRTGRRPKPEIMASKEQQIQRDDPGAS PQSSSQPD  
HGRLSPPEAPDRPTISTASETSVYVTWIPRGNGGFPIQSFRVEYKKLKKVGDWILATSAI  
PPSRLSVEITGLEKGT SYKFRVRALNMLGESEPSAPSRPYVVS GYSGRVYERP VAGPYIT  
FTDAVNETTIMLKWMIIPASNNNTPIHGFYIYYRPTSDSDNDSYKKDMVEGD KYWHSISH  
LQPETSYDIKMQCFNEGGESEFSNVMICETKARKSSGQPGRLPPPTLAPPQPPLPETIER  
PVG TGAMVARSSDLPYLIIVGVVLGSI VLIIVTFIPFCLWRAW SKQKHTTDLGFPR SALPP  
SCPYTMVPLGGLPGHQASGQPYLSGISGRACANGIHMNRGCPSAAVGYPGMKPQQHCPGE  
LQQQSDTSSLLRQTHLGNGYDPQSHQITRGPKSSPDEGSFLYTL PDDSTHQLLQPHHDCC  
QRQE QPAAVGQSGVRRAPDSPVLEAVWDPPFHSGPPCCLGLVPVEEVDSPDSCQVSGGDW  
CPQHVPV GAYVQGEPGMQLSPGPLVRVSFETPPLTI

**Signal peptide:**  
amino acids 1-30

**Transmembrane domain:**  
amino acids 16-30 (type II), 854-879

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## FIGURE 159

CCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCGTCCG  
CCCACGCGTCCGCCCACGCGTCCGGTGCAAGCTCGCGCCGCACACTGCCTGGTGGAGGGA  
AGGAGCCCCGGGCGCCTCTCGCCGCTCCCCGCGCCGCGTCCGCACCTCCCCACCGCCCGC  
CGCCCCGCGCCCGCCGCCCCGCAAAGCATGAGTGAGCCCGCTCTCTGCAGCTGCCCGGGGC  
GCGAATGGCAGGCTGTTTCCGCGGAGTAAAGGTGGCGCCGGTCAGTGGTCGTTTCCAAT  
GACGGACATTAACCAGACTGTCAGATCCTGGGGAGTCGCGAGCCCCGAGTTTGGAGTTTT  
TTCCCCCCCACAACGTACAGTCCGAAGTGCAGAGGGAAAGGAAGGCGGCAGGAAGGCGAA  
GCTCGGGCTCCGGCACGTAGTTGGGAAACTTGCGGGTCTAGAAAGTCGCCTCCCCGCCTT  
GCCGGCCGCCCTTGACAGCCCCGAGCCGAGCAGCAAAGTGAGACATTGTGCGCTGCCAGA  
TCCGCCGCGCCGCGGACCGGGGCTGCCTCGGAAACACAGAGGGGTCTTCTCTCGCCCTGCA  
TATAATTAGCCTGCACACAAAGGGAGCAGCTGAATGGAGGTTGTCACTCTCTGGAAAAGG  
ATTTCTGACCGAGCGCTTCCAATGGACATTCTCCAGTCTCTCTGGAAAGATTCTCGCTAA  
TGGATTTCTCTGCTGCTCGGTCTCTGTCTATACTGGCTGCTGAGGAGGCCCTCGGGGGTGG  
TCTTGTGTCTGCTGGGGGCTGCTTTTCAAGTGTGCTGCCCCGCCGCCCCAGCGGGTGCCCGC  
AGCTGTGCCGGTGCGAGGGGCGGTGCTGTACTGCGAGGCGCTCAACCTCACCGAGGCGC  
CCCACAACCTGTCCGGCCTGCTGGGCTTGTCCCTGCGCTACAACAGCCTCTCGGAGCTGC  
GCGCCGCGCAGTTCACGGGGTTAATGCAGCTCACGTGGCTCTATCTGGATCACAATCACA  
TCTGCTCCGTGCAGGGGGACGCCTTTTCAAGAACTGCGCCGAGTTAAGGAACCTCACGTGA  
GTTCCAACCAGATCACCCAACCTGCCAACACCACTTCCGGCCCATGCCAACCTGCGCA  
GCGTGACCTCTCGTACAACAAGCTGCAGGCGCTCGCGCCCGACCTCTTCCACGGGCTGC  
GGAAGCTCACACGCTGCATATGCGGGCCAACGCCATCCAGTTTGTGCCCCGTGCGCATCT  
TCCAGGACTGCCGAGCCTCAAGTTTCTCGACATCGGATACAATCAGCTCAAGAGTCTGG  
CGCGCAACTCTTTCGCCGGCTTGTTTAAAGCTCACCGAGCTGCACCTCGAGCACAACGACT  
TGGTCAAGGTGAACCTTCCCCGCGCCTCATCTCCCTGCACTCGCTCTGCCTGC  
GGAGGAACAAGGTGGCCATTGTGGTCAGCTCGCTGGACTGGGTTTGGAACTGGAGAAAA  
TGGACTTGTGCGGGCAACGAGATCGAGTACATGGAGCCCCATGTGTTGAGACCGTGCCGC  
ACCTGCAGTCCCTGCAGCTGGACTCCAACCGCCTCACCTACATCGAGCCCCGGATCCTCA  
ACTCTTGGAAGTCCCTGACAAGCATCACCTGGCCGGGAACCTGTGGGATTGCGGGCGCA  
ACGTGTGTGCCCTAGCCTCGTGGCTCAGCAACTTCCAGGGGCGCTACGATGGCAACTTGC  
AGTGCGCCAGCCCGGAGTACGCAACAGGGCGAGGACGTCTTGACGCGGTGTACGCCTTCC  
ACCTGTGCGAGGATGGGGCCGAGCCCAACAGCGGCCACCTGCTCTCGGCCGTACCAACC  
GCAGTGATCTGGGGCCCCCTGCCAGCTCGGCCACCAGCTCGCGGACGGCGGGGAGGGGC  
AGCACGACGGCACATTTCGAGCCTGCCACCGTGGCTCTTCCAGGCGGCGAGCACGCCGAGA  
ACGCCGTGCAGATCCACAAGGTGGTCACGGGCACCATGGCCCTCATCTTCTCCTTCTCTCA  
TCGTGGTCTTGGTGCTCTACGTGTCTTGGAAAGTGTTCCTCCAGCCAGCCTCAGGCAGCTCA  
GACAGTGCTTTGTACGCGAGCGCAGGAAGCAAAAGCAGAAACAGACCATGCATCAGATGG  
CTGCCATGTCTGCCAGGAATACTACGTTGATTACAAACCGAACCACATTGAGGGAGCCC  
TGGTGATCATCAACGAGTATGGCTCGTGTACCTGCCACCAGCAGCCCGCGAGGGAATGCG  
AGGTGTGAATTGTCCAGTGGCTCTCAACCCATGCGCTACCAAATACGCCTGGGCAGCCGG  
GACGGGCCGGCGGGCACCAGGCTGGGGTCTCCTTGTCTGTGCTCTGATATGCTCCTTGAC  
TGAAACTTTAAGGGGATCTCTCCAGAGACTTGACATTTTAGCTTTATTGTGTCTTAAAA  
ACAAAAGCGAATTAAAAACACAACAAAAAACCCACCCCAACCTTCAGGACAGTCTATC  
TTAAATTTTATATGAGAACTCCTTCCCTCCCTTTGAAGATCTGTCCATATTAGGAATCTG  
AGAGTGTAATAAAGGTGGCCATAAGACAGAGAGAGAATAATCGTGCTTTGTTTTATGCTA  
CTCCTCCACCCCTGCCCATGATTAAACATCATGTATGTAGAAGATCTTAAGTCCATACGC  
ATTTTCATGAAGAACCATTGGAAAGAGGAATCTGCAATCTGGGAGCTTAAGAGCAAATGAT

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GACCATAGAAAGCTATGTTCTTACTTTGTGTGTGTGTCTGTATGTTTCTGCGTTGTGTGT  
CTTTGTAGGCAAGCAAACGTTGTCTACACAAACGGGAATTTAGCTCACATCATTTTCATGC  
CCCTGTGCCTCTAGCTCTGGAGATTGGTGGGGGGAGGTGGGGGGAAACGGCAGGAATAAG  
GGAAAGTGGTAGTTTTTAAGGTTTGTAACTTGAATCTTTTCTTCTCAAATTA  
ATTATCTTTAAGCTTCAAGAACTTGCTCTGACCCCTCTAAGCAAACCTACTAAGCATTTA  
AAAGAGAATCTAATTTTTTAAAGGTGTAGCACCTTTTTTTTTTATTCTTCCACAGAGGGTG  
CTAATCTCATTATGCTGTGCTATCTGAAAAGAACTTAAGGCCACAATTCACGTCTCGTCC  
TGGGCATTGTGATGGATTGACCCTCCATTTGCAGTACCTTCCCAGCTGATTAAAGTTCAG  
CAGTGGTATTGAGGTTTTTCGAATATTTATATAGAAAAAAGTCTTTTCACATGACAAAT  
GACACTCTCACACCAGTCTTAGCCCTAGTAGTTTTTTTAGGTTGGACCAGAGGAAGCAGGT  
TAAATGAGACCTGTCCTCTGCTGCACTCAGAAAAAATAGGCAGTCCCTGATGCTCAGATC  
TTAGCCTTGATATTAATAGTTGAGACCACCTACCCACAATGCAGCCTATACTCCCAAGAC  
TACAAAGTTACCATCGCAAAGGAAAGGTTATTCCAGTAAAAGGAAATAGTTTTCTCAACC  
ATTTAAAAATATTCTTCTGAACTCATCAAAGTAGAAGAGCCCCAACCTTTTCTCTCTGC  
CTTCAAGAAGGCAGACATTTGGTATGATTTAGCATCAACAACACATTTATGAGTATATGT  
AAGTAATCAGAGGGGCAAATGCCACTTGTTATTCCTCCCAAGTTTTCCAAGCAAGTACAC  
ACAGATCTCTGGTAGGATTAGGGGCCACTTGTGTTTTCCGGCTTATTTTAGTCGACTTGTC  
AGCAAGTTTGATGCCTAGTCTATCTGACATGGCCCAGTAGAACAGGGCATTGATGGATCA  
CATGAGATGGTAGAAGGAACATCATCACATACCCCTCTCACAGAGAAAATTATCAAAGAA  
CCAGAAATTATATCTGTTTTGGAGCAAGAGTGTATAATGTTTCAGGGTAGTCAAATAA  
ACATAAATTATCTCCTCTAGATGAGTGGCGATGTTGGCTGATTTGGGTCTGCCATTGACA  
GAATGTCAAATAAAAAGGAATTAGCTAGAATATGACCATTAAATGTGCTTCTGAAATATA  
TTTTGAGATAGGTTTAGAATGTCA



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**FIGURE 160**

MDFLLLGLCLYWLLRRPSGVVLCLLGACFQMLPAAPSGCPQLCRCEGRLLYCEALNLTEA  
PHNLSGLLGLSLRYNSLSELRAGQFTGLMQLTWLYLDHNHICSVQGDAFQKLRRVKELTL  
SSNQITQLPNTTFRPMPNLRSDLSYNKLQALAPDLFHGLRKLTTLHMRANAIQFVPVRI  
FQDCRSKFLDIGYNQLKSLARNSFAGLFKLTEHLEHNDLVKVNFAHFPRILSLHSLCL  
RRNKVAIVSSLDWVWNLEKMDLSGNEIEMEYPHVFEVPHLQSLQLDSNRLTYIEPRIL  
NSWKSITSITLAGNLWDCGRNVCALASWLSNFQGRYDGNLQCASPEYAQGEDVLDVYAF  
HLCEDGAEPSTGHLLSAVTNRSDLGPPASSATTADGGEGQHDGTFEPATVALPGGEHAE  
NAVQIHKVVTGTMALIFSLIVVLVLYVSWKCFPASLRQLRQCFVTQRRKQKQKQTMHQM  
AAMSAQEYYVDYKPNHIEGALVIINEYGSCTCHQQPARECEV



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**FIGURE 162**

MAPQSLPSSRMAPLGMLLGLLMAACFTFCLSHQNLKEFALTNPEKSSTKETERKETKAEE  
ELDAEVLEVFPHTHEWQALQPGQAVPAGSHVRLNLQTGEREAKLOYEDKFRNNLKGKRLD  
INTNTYTSQDLKSALAKFKEGAEMESSKEDKARQAEVKRLFRPIEELKKDFDELNVVIET  
DMQIMVRLINKFNSSSSSLEEKIAALFDLEYVYVHQMDNAQDLLSFGGLQVVINGLNSTEP  
LVKEYAAFVVLGAAFSSNPKVQVEAIEGGALQKLLVILATEQPLTAKKKVLFALCSLLRHF  
PYAQRQFLKLGGGLQVLRITLVQEKGTEVLAVRVVTLTYDLVTEKMFEEEEAELTQEMSPEK  
LQQYRQVHLLPGLWEQGWCEITAHLLALPEHDAREKVLQTLGVLLTTCDRYRQDPQLGR  
TLASLQAEYQVLASLELQDGEDEGYFQELLGSVNSLLKELR

**Important features:**

**Signal peptide:**

amino acids 1-29

**Hypothetical YJL126w/YLR351c/yhcX family protein:**

amino acids 364-373

**N-glycosylation site:**

amino acids 193-197, 236-240

**N-myristoylation site:**

amino acids 15-21, 19-25, 234-240, 251-257, 402-408, 451-457

**Homologous region SLS1 protein:**

amino acids 68-340

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**FIGURE 163**

CAGAGAGGAGGCTTTGGGAATTGTCCAGCAGAAACAGAGAAGTCTGAGGTGGTGTCAAGA  
CAAAAGATGCTTCAGCTTTGGAACTTGTTCTCCTGTGCGGCGTGCTCACTGGGACCTCA  
GAGTCTCTTCTTGACAATCTTGGCAATGACCTAAGCAATGTCGTGGATAAGCTGGAACCT  
GTTCTTCACGAGGGACTTGAGACAGTTGACAATACTCTTAAAGGCATCCTTGAGAACTG  
AAGGTCGACCTAGGAGTGCTTCAGAAATCCAGTGCTTGGCAACTGGCCAAGCAGAAGGCC  
CAGGAAGCTGAGAAATTGCTGAACAATGTCATTTCTAAGCTGCTTCCAACCTAACACGGAC  
ATTTTTGGGTTGAAAATCAGCAACTCCCTCATCCTGGATGTCAAAGCTGAACCGATCGAT  
GATGGCAAAGGCCTTAACCTGAGCTTCCCTGTCAACGCGAATGTCACTGTGGCCGGGCCC  
ATCATTGGCCAGATTATCAACCTGAAAGCCTCCTTGGACCTCCTGACCGCAGTCACAATT  
GAAACTGATCCCCAGACACACCAGCCTGTTGCCGTCTTGGGAGAATGCGCCAGTGACCCA  
ACCAGCATCTCACTTTCCTTGCTGGACAAACACAGCCAAATCATCAACAAGTTCGTGAAT  
AGCGTGATCAACACGCTGAAAAGCACTGTATCCTCCCTGCTGCAGAAGGAGATATGTCCA  
CTGATCCGCATCTTCATCCACTCCCTGGATGTGAATGTCATTTCAGCAGGTTCGTGCATAAT  
CCTCAGCACAAAACCCAGCTGCAAACCCTCATCTGAAGAGGACGAATGAGGAGGACCACT  
GTGGTGATGCTGATTGGTTCCAGTGCTTGCCCCACCCCCTTATAGCATCTCCCTCCA  
GGAAGCTGCTGCCACCACCTAACCAGCGTGAAAGCCTGAGTCCCACCAGAAGGACCTTCC  
CAGATACCCCTTCTCCTCACAGTCAGAACAGCAGCCTCTACACATGTTGTCTGCCCCTG  
GCAATAAAGGCCCATTTCTGCACCCTTAA

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**FIGURE 164**

MLQLWKLVLLCGVLTGTSESLLDNLGNDLSNVVDKLEPVLHEGLETVDNTLKGILEKLV  
DLGVLQKSSAWQLAKQKAQEAELLNNVISKLLPTNTDIFGLKISNSLILDVKAEPIDG  
KGLNLSFPVTANVTVAGPIIGQIINLKASDLLTAVTIETDPQTHQPVAVLGECDPTS  
ISLSLLDKHSQIINKFVNSVINTLKSTVSSLLQKEICPLIRIFIHSLDVNVIQQVVDNPQ  
HKTQLQTLI

**Important features:****Signal peptide:**

1-15

**Transmembrane domain:**

none

**N-glycosylation site:**

124-128, 132-136

**N-myristoylation site:**

12-18, 16-22, 26-32, 101-107, 122-128, 141-147

**Leucine zipper pattern:**

44-66

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**FIGURE 165**

GCAGTCAGAGACTTCCCCTGCCCCCTCGCTGGGAAAGAACATTAGGAATGCCTTTTATGTGC  
CTTGCTTTCCTGAACTAGCTCACAGTAGCCCGGCGGCCAGGGCAATCCGACCACATTTCA  
CTCTCACCGCTGTAGGAATCCAGATGTCAGGCCAAGTACAGCAGCACGAGGGACATGCTGG  
ATGATGATGGGGACACCACCATGAGCCTGCATTCTCAAGCCTCTGCCACAACCTCGGCATC  
CAGAGCCCCGGCGCACAGAGCACAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGA  
CCCTGCTGACTTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTT  
TTCAGTACTACCAGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGAT  
TAGGAAATACGTCCCAAGAGTTGCAATCTCTTCAAGTCCAGAATATAAAGCTTGCAGGAA  
GTCTGCAGCATGTGGCTGAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGCACACA  
GGTGCAGCCCTTGTACAGAACAATGGAAATGGCATGGAGACAATTGCTACCAGTTCTATA  
AAGACAGCAAAAGTTGGGAGGACTGTAAATATTTCTGCCTTAGTGAAAACCTTACCATGC  
TGAAGATAAACAAACAAGAAGACCTGGAATTTGCCGCGTCTCAGAGCTACTCTGAGTTTT  
TCTACTCTTATTGGACAGGGCTTTTGCGCCCTGACAGTGGCAAGGCCTGGCTGTGGATGG  
ATGGAACCCCTTTCACTTCTGAACTGTTCCATATTATAATAGATGTCACCAGCCCAAGAA  
GCAGAGACTGTGTGGCCATCCTCAATGGGATGATCTTCTCAAAGGACTGCAAAGAATTGA  
AGCGTTGTGTCTGTGAGAGAAGGGCAGGAATGGTGAAGCCAGAGAGCCTCCATGTCCCCC  
CTGAAACATTAGGCGAAGGTGACTGATTTCGCCCTCTGCAACTACAAATAGCAGAGTGAGC  
CAGGCGGTGCCAAAGCAAGGGCTAGTTGAGACATTGGGAAATGGAACATAATCAGGAAAG  
ACTATCTCTCTGACTAGTACAAAATGGGTCTCTCGTGTTTCCTGTTTCAGGATCACCAGCAT  
TTCTGAGCTTGGGTTTTATGCACGTATTTAACAGTCAACAAGAAGTCTTATTTACATGCCAC  
CAACCAACCTCAGAAACCCATAATGTCATCTGCCTTCTTGGCTTAGAGATAACTTTTAGC  
TCTCTTTCTTCTCAATGTCTAATATCACCTCCCTGTTTTTCATGTCTTCCTTACACTTGGT  
GGAATAAGAACTTTTTTGAAGTAGAGGAAATACATTGAGGTAACATCCTTTTCTCTGACA  
GTCAAGTAGTCCATCAGAAATTGGCAGTCACCTCCAGATTGTACCAGCAAATACACAAG  
GAATTCTTTTTTGTGTTTTCAGTTCATACTAGTCCCTTCCCAATCCATCAGTAAAGACCC  
CATCTGCCTTGTCCATGCCGTTTCCCAACAGGGATGTCACTTGATATGAGAATCTCAAAT  
CTCAATGCCTTATAAGCATTCCTTCTGTGTCCATTAAGACTCTGATAATTGTCTCCCT  
CCATAGGAATTTCTCCAGGAAAGAAATATATCCCATCTCCGTTTCATATCAGAACTAC  
CGTCCCCGATATTCCCTTCAGAGAGATTAAAGACCAGAAAAAAGTGAGCCTCTTCATCTG  
CACCTGTAATAGTTTCAGTTCCTATTTTCTTCCATTGACCCATATTTATACCTTTCAGGT  
ACTGAAGATTTAATAATAATAAATGTAAATACTGTGAAAAA

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**FIGURE 166**

MQAKYSSTRDMLDDDGD TTMSLHSQASATTRHPEPRRTEHRAPSSTWRPVALTLLTLCLV  
LLIGLAALGLLFFQYYQLSNTGQDTISQMEERLGNTSQELQSLQVQNIKLAGSLQHVAEK  
LCRELYNKAGAHRCSPCTEQWKWHGDNCYQFYKDSKSWEDCKYFCLSENSTMLKINKQED  
LEFAASQSYSEFFYSYWTGLLRPD SGKAWLWMDGTPFTSELFHIIIDVTSPRSRDCVAIL  
NGMIFSKDCKELKRCVCERRAGMVKPESLHVPPETLGED

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**FIGURE 167**

CGGACGGGCAGGACGCCCCGTTTCGCCTAGCGCGTGCTCAGGAGTTGGTGTCTGCCTGCG  
CTCAGGATGAGGGGGAATCTGGCCCTGGTGGGCGTTCTAATCAGCCTGGCCTTCCTGTCA  
CTGCTGCCATCTGGACATCCTCAGCCGGCTGGCGATGACGCCTGCTCTGTGCAGATCCTC  
GTCCCTGGCCTCAAAGGGGATGCGGGAGAGAAGGGAGACAAAGGCGCCCCCGGACGGCCT  
GGAAGAGTCGGCCCCACGGGAGAAAAAGGAGACATGGGGGACAAAGGACAGAAAGGCAGT  
GTGGGTCGTTCATGGAAAAATTGGTCCCATTGGCTCTAAAGGTGAGAAAGGAGATTCCGGT  
GACATAGGACCCCCTGGTCCTAATGGAGAACCAGGCCTCCCATGTGAGTGCAGCCAGCTG  
CGCAAGGCCATCGGGGAGATGGACAACCAGGTCTCTCAGCTGACCAGCGAGCTCAAGTTC  
ATCAAGAATGCTGTGCGCCGTGTGCGCGAGACGGAGAGCAAGATCTACCTGCTGGTGAAG  
GAGGAGAAGCGCTACGCGGACGCCCAGCTGTCCTGCCAGGGCCGCGGGGGCACGCTGAGC  
ATGCCCAAGGACGAGGCTGCCAATGGCCTGATGGCCGCATACCTGGCGCAAGCCGGCCTG  
GCCCCTGTCTTCATCGGCATCAACGACCTGGAGAAGGAGGGCGCCTTCGTGTACTCTGAC  
CACTCCCCCATGCGGACCTTCAACAAGTGGCGCAGCGGTGAGCCCAACAATGCCTACGAC  
GAGGAGGACTGCGTGGAGATGGTGGCCTCGGGCGGCTGGAACGACGTGGCCTGCCACACC  
ACCATGTACTTCATGTGTGAGTTTGACAAGGAGAACATGTGAGCCTCAGGCTGGGGCTGC  
CCATTGGGGGCCCCACATGTCCCTGCAGGGTTGGCAGGGACAGAGCCCAGACCATGGTGC  
CAGCCAGGGAGCTGTCCCTCTGTGAAGGGTGGAGGCTCACTGAGTAGAGGGCTGTTGTCT  
AAACTGAGAAAATGGCCTATGCTTAAGAGGAAAATGAAAGTGTTCTGGGGTGCTGTCTC  
TGAAGAAGCAGAGTTTCATTACCTGTATTGTAGCCCCAATGTCATTATGTAATTATTACC  
CAGAATTGCTCTTCCATAAAGCTTGTGCCTTTGTCCAAGCTATACAATAAAATCTTTAAG  
TAGTGCAGTAGTTAAGTCCAAAAAAAAAAAAAAAAAAAAA



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**FIGURE 168**

MRGNLALVGVLISLAFLSLLPSGHPQPAGDDACSVQILVPGLKGDAGEKGDKGAPGRPGR  
VGPTGEKGDMDKGQKGSVGRHGKIGPIGSKGEKGDSDIGPPGPNGEPGLPCECSQLRK  
AIGEMDNQVSQLTSELKFIKNAVAGVRETESKIYLLVKEEKRYADAQLSCQGRGGTLSMP  
KDEAANGLMAAYLAQAGLARVFIGINDLEKEGAFVYSDHSPMRTFNKWRSGEPNNAYDEE  
DCVEMVASGGWNDVACHTTMYFMCEFDKENM

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**FIGURE 169**

AGTGACTGCAGCCTTCCTAGATCCCCTCCACTCGGTTTCTCTCTTTGCAGGAGCACCGGC  
AGCACCAGTGTGTGAGGGGAGCAGGCAGCGGTCTAGCCAGTTCCTTGATCCTGCCAGAC  
CAGCCAGCCCCCGGCACAGAGCTGCTCCACAGGCACCAATGAGGATCATGCTGCTATTAC  
AGCCATCCTGGCCTTCAGCCTAGCTCAGAGCTTTGGGGCTGTCTGTAAGGAGCCACAGGA  
GGAGGTGGTTCTTGGCGGGGGCCGCAGCAAGAGGGATCCAGATCTCTACCAGCTGCTCCA  
GAGACTCTTCAAAAGCCACTCATCTCTGGAGGGATTGCTCAAAGCCCTGAGCCAGGCTAG  
CACAGATCCTAAGGAATCAACATCTCCCGAGAAACGTGACATGCATGACTTCTTTGTGGG  
ACTTATGGGCAAGAGGAGCGTCCAGCCAGAGGGAAAGACAGGACCTTTCTTACCTTCAGT  
GAGGGTTCCTCGGCCCCCTTCATCCCAATCAGCTTGGATCCACAGGAAAGTCTTCCCTGGG  
AACAGAGGAGCAGAGACCTTTATAAGACTCTCCTACGGATGTGAATCAAGAGAACGTCCC  
CAGCTTTGGCATCCTCAAGTATCCCCCGAGAGCAGAATAGGTACTCCACTTCCGGAATCC  
TGGACTGCATTAGGAAGACCTCTTTCCCTGTCCCAATCCCCAGGTGCGCACGCTCCTGTT  
ACCCTTTCTCTTCCCTGTTCTTGTAACATTCTTGCTTTGACTCCTTCTCCATCTTTTC  
TACCTGACCCTGGTGTGGAACTGCATAGTGAATATCCCCAACCCCAATGGGCATTGACT  
GTAGAATACCCTAGAGTTCCTGTAGTGTCTACATTAAAAATATAATGTCTCTCTCTATT  
CCTCAACAATAAAGGATTTTTGCATATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAA

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**FIGURE 170**

MRIMLLFTAILAFSLAQSFQAVCKEPQEEVVPGGGRSKRDPDLYQLLQRLFKSHSSLEGL  
LKALSQASTDPKESTSPKRDMDHDFVGLMGKRSVQPEGKTGPFLPSVRVPRPLHPNQLG  
STGKSSLGTEEQRPL

**Important features:**

**Signal peptide:**

amino acids 1-18

**Tyrosine kinase phosphorylation site:**

amino acids 36-45

**N-myristoylation site:**

amino acids 33-39, 59-65

**Amidation site:**

amino acids 90-94

**Leucine zipper pattern:**

amino acids 43-65

**Tachykinin family signature:**

amino acids 86-92

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**FIGURE 171**

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTAAGCA  
GGCAGTGTTTTGCCTTCACCCCAAGTGACCATGAGAGGTTGCCACGCGAGTCTCAATCATG  
CTCCTCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATGTC  
CAGTGTGGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGC  
ACCCCGCTGGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTC  
AGGAAACGCAAGCACACACCTGTCCTTGCTTGCCCAACCTGCTGTGCTCCAGGTTCCCG  
GACGGCAGGTACCGCTGCTCCATGGACTTGAAGAACATCAATTTTTTAGGCGCTTGCCTGG  
TCTCAGGATACCCACCATCCTTTTCCTGAGCACAGCCTGGATTTTTATTTCTGCCATGAA  
ACCCAGCTCCCATGACTCTCCAGTCCCTACACTGACTACCCTGATCTCTCTTGTCTAGT  
ACGCACATATGCACACAGGCAGACATACCTCCCATCATGACATGGTCCCCAGGCTGGCCT  
GAGGATGTACAGCTTGAGGCTGTGGTGTGAAAGGTGGCCAGCCTGGTTCTCTTCCCTGC  
TCAGGCTGCCAGAGAGGTGGTAAATGGCAGAAAGGACATTCCCCCTCCCCTCCCCAGGTG  
ACCTGCTCTCTTTCTGGGCCCTGCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAG  
ACATTCTGGGCACAGGCTCTTGGGTGCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCC  
TCAGGCCCTTCACGTGAGGTCTGTGAGGACCAATTTGTGGGTAGTTCATCTTCCCTCGAT  
TGGTTAACTCCTTAGTTTCAGACCACAGACTCAAGATTGGCTCTTCCCAGAGGGCAGCAG  
ACAGTCACCCCAAGGCAGGTGTAGGGAGCCCAGGGAGGCCAATCAGCCCCCTGAAGACTC  
TGGTCCCAGTCAGCCTGTGGCTTGTGGCCTGTGACCTGTGACCTTCTGCCAGAATTGTCA  
TGCCTCTGAGGCCCCCTCTTACCACACTTTACCAGTTAACCCTGAAGCCCCCAATTCCC  
ACAGCTTTTCCATTAAAATGCAAATGGTGGTGGTTCAATCTAATCTGATATTGACATATT  
AGAAGGCAATTAGGGTGTTTCCTTAAACAACCTCTTTCCAAGGATCAGCCCTGAGAGCAG  
GTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGGTGGGAGCAAGGGACAGGG  
AGCAGGGCAGGGGCTGAAAGGGGCCTGATTGAGACCAGGGAGGCAACTACACACCAACA  
TGCTGGCTTTAGAATAAAAGCACCAACTGAAAAA

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## FIGURE 172

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEEC  
HPGSHKVPFFRK RKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

**Signal peptide:**  
amino acids 1-19

**Tyrosine kinase phosphorylation site:**  
amino acids 88-95

**N-myristoylation sites:**  
amino acids 33-39, 35-41, 46-52

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**FIGURE 173**

AGCGCCCGGGCGTCGGGGCGGTAAAAGGCCGGCAGAAGGGAGGCACTTGAGAAATGTCTT  
TCCTCCAGGACCCAAGTTTCTTCACCATGGGGATGTGGTCCATTGGTGCAGGAGCCCTGG  
GGGCTGCTGCCTTGGCATTGCTGCTTGCCAACACAGACGTGTTTCTGTCCAAGCCCCAGA  
AAGCGGCCCTGGAGTACCTGGAGGATATAGACCTGAAAACACTGGAGAAGGAACCAAGGA  
CTTTCAAAGCAAAGGAGCTATGGGAAAAAAATGGAGCTGTGATTATGGCCGTGCGGAGGC  
CAGGCTGTTTCTCTGTGCGAGAGGAAGCTGCGGATCTGTCTCCCTGAAAAGCATGTTGG  
ACCAGCTGGGCGTCCCCCTCTATGCAGTGGTAAAGGAGCACATCAGGACTGAAGTGAAGG  
ATTTCCAGCCTTATTTCAAAGGAGAAATCTTCCTGGATGAAAAGAAAAAGTTCTATGGTC  
CACAAAGGCGGAAGATGATGTTTATGGGATTTATCCGTCTGGGAGTGTGGTACAACCTTCT  
TCCGAGCCTGGAACGGAGGCTTCTCTGGAACCTGGAAGGAGAAGGCTTCATCCTTGGGG  
GAGTTTTCGTGGTGGGATCAGGAAAGCAGGGCATTCTTCTTGAGCACCGAGAAAAAGAAT  
TTGGAGACAAAGTAAACCTACTTTCTGTTCTGGAAGCTGCTAAGATGATCAAACCAACAGA  
CTTTGGCCTCAGAGAAAAAAATGATTTGTGTGAAACTGCCCAGCTCAGGGATAACCAGGGAC  
ATTCACCTGTGTTTCATGGGATGTATTGTTTCCACTCGTGTCCCTAAGGAGTGAGAAACCC  
ATTTATACTCTACTCTCAGTATGGATTATTAATGTATTTTAATATTCTGTTTAGGCCAC  
TAAGGCAAAATAGCCCCAAAACAAGACTGACAAAAATCTGAAAACTAATGAGGATTATT  
AAGCTAAAACCTGGGAAATAGGAGGCTTAAAATTGACTGCCAGGCTGGGTGCAGTGGCTC  
ACACCTGTAATCCCAGCACTTTGGGAGGCCAAGGTGAGCAAGTCACTTGAGGTCGGGAGT  
TCGAGACCAGCCTGAGCAACATGGCGAAACCCCGTCTCTACTAAAAATACAAAAATCACC  
CGGGTGTGGTGGCAGGCACCTGTAGTCCCAGCTACCCGGGAGGCTGAGGCAGGAGAATCA  
CTTGAACCTGGGAGGTGGAGGTTGCGGTGAGCTGAGATCACACCACTGTATTCCAGCCTG  
GGTGA CTGAGACTCTAACTAA

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**FIGURE 174**

MSFLQDPSFFTGMWWSIGAGALGAAALALLANTDVFLSKPQKALEYLEDIDLKTLEKE  
PRTFKAKELWEKNGAVIMAVRRPGCFLCREEAADLSSLKSMLDQLGVPLYAVVKEHIRTE  
VKDFQPYFKGEIFLDEKKKFYGPQRRKMMFMGFIRLGWYNFFRAWNGGFSGNLEGEGLFI  
LGGVFVVGSGKQGILLEHREKEFGDKVNLLSVLEAAKMIKPQTLASEKK

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**FIGURE 175**

GACAGTGGAGGGCAGTGGAGAGGACCGCGCTGTCCTGCTGTCACCAAGAGCTGGAGACAC  
CATCTCCCACCGAGAGTCAATGGCCCCATTGGCCCTGCACCTCCTCGTCCTCGTCCCCATC  
CTCCTCAGCCTGGTGGCCTCCCAGGACTGGAAGGCTGAACGCAGCCAAGACCCCTTCGAG  
AAATGCATGCAGGATCCTGACTATGAGCAGCTGCTCAAGGTGGTGACCTGGGGGCTCAAT  
CGGACCCTGAAGCCCCAGAGGGTGATTGTGGTTGGCGCTGGTGTGGCCGGGCTGGTGGCC  
GCCAAGGTGCTCAGCGATGCTGGACACAAGGTACCATCCTGGAGGCAGATAACAGGATC  
GGGGGCCGCATCTTACCTACCGGGACCAGAACACGGGCTGGATTGGGGAGCTGGGAGCC  
ATGCGCATGCCCAGCTCTCACAGGATCCTCCACAAGCTCTGCCAGGGCCTGGGGCTCAAC  
CTGACCAAGTTCACCCAGTACGACAAGAACACGTGGACGGAGGTGCACGAAGTGAAGCTG  
CGCAACTATGTGGTGGAGAAGGTGCCCCGAGAAGCTGGGCTACGCCTTGCGTCCCCAGGAA  
AAGGGCCACTCGCCCGAAGACATCTACCAGATGGCTCTCAACCAGGGCCCTCAAAGACCTC  
AAGGCCTGGGCTGCAGAAAGGCGATGAAGAAGTTTGAAGGCACACGCTCTTGGAATAT  
CTTCTCGGGGAGGGGAACCTGAGCCGGCCGGCCGTGCAGCTTCTGGGAGACGTGATGTCC  
GAGGATGGCTTCTTCTATCTCAGCTTCGCCGAGGCCCTCCGGGCCCACAGCTGCCTCAGC  
GACAGACTCCAGTACAGCCGCATCGTGGGTGGCTGGGACCTGCTGCCGCGCGCGCTGCTG  
AGCTCGCTGTCCGGGCTTGTGCTGTTGAACGCGCCCCGTGGTGGCGATGACCCAGGGACCG  
CACGATGTGCACGTGCAGATCGAGACCTCTCCCCCGCGCGGAATCTGAAGGTGCTGAAG  
GCCGACGTGGTGCTGCTGACGGCGAGCGGACCGGCGGTGAAGCGCATCACCTTCTCGCCG  
CCGCTGCCCCGCCACATGCAGGAGGCGCTGCGGAGGCTGCACTACGTGCCGGCCACCAAG  
GTGTTCCCTAAGCTTCCGCAGGCCCTTCTGGCGCGAGGAGCACATTGAAGGCGGCCACTCA  
AACACCGATCGCCCGTCGCGCATGATTTTCTACCCGCCGCCGCGCGAGGGCGCGCTGCTG  
CTGGCCTCGTACACGTGGTTCGGACGCGGCGGCAGCGTTTCGCCGGCTTGAGCCGGGAAGAG  
GCGTTGCGCTTGGCGCTCGACGACGTGGCGGCATTGCACGGGCCTGTCTGTGCGCCAGCTC  
TGGGACGGCACCCGGCGTCTCAAGCGTTGGGCGGAGGACCAGCACAGCCAGGGTGGCTTT  
GTGGTACAGCCGCCGGCGCTCTGGCAAACCGAAAAGGATGACTGGACGGTCCCTTATGGC  
CGCATCTACTTTGCCGGCGAGCACACCGCCTACCCGCACGGCTGGGTGGAGACGGCGGT  
AAGTCGGCGCTGCGCGCCGCCATCAAGATCAACAGCCGGAAGGGGCTGCATCGGACACG  
GCCAGCCCCGAGGGGCACGCATCTGACATGGAGGGGCAGGGGCATGTGCATGGGGTGGCC  
AGCAGCCCCCTCGCATGACCTGGCAAAGGAAGAAGGCAGCCACCCTCCAGTCCAAGGCCAG  
TTATCTCTCCAAAACACGACCCACACGAGGACCTCGCATTAAAGTATTTTCGGAAAAAA  
AA



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**FIGURE 176**

MAPLALHLLVLVPILLSLVASQDWKAERSQDPFEKCMQDPDYEQLLKVVWGLNRTLKPQ  
RVIVVGAGVAGLVAAKVLSDAGHKVTILEADNRIGGRIFTYRDQNTGWIGELGAMRMPSS  
HRILHKLCQGLGLNLTKFTQYDKNTWTEVHEVKLRNYVVEKVPEKLGALRPQEKGHSPE  
DIYQMALNQALKDLKALGCRKAMKKFERHTLLEYLLGEGNLSRPAVQLLGDMSEDGFFY  
LSFAEALRAHSCLSDRLQYSRIVGGWDLPRALLSSLSGLVLLNAPVVAMTQGPHDVHVQ  
IETSPPARNLKVLKADVLLTASGPAVKRITFSPPLPRHMQEALRRLHYVPATKVFLSFR  
RPFWREEHIEGGHSNTDRPSRMIFYPPPREGALLLASYTWSDAFAAGLSREEALRLAL  
DDVAALHGPVVRQLWDGTGVVKRWAEDQHSQGGFVVQPPALWQTEKDDWTVPYGRIYFAG  
EHTAYPHGWVETAVKSALRAAIKINSRKGPASDTASPEGHASDMEGQGHVHGVAASSPSHD  
LAKEEGSHPPVQGQLSLQNTTHTRTSH

**Signal peptide:**  
amino acids 1-21

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**FIGURE 177**

CCGGGGAGGGGAGGGCCCCGTCCCGCCCCCTCCCCGTCTCTCCCCGCCCCCTCCCCGTCCCTC  
CCGCCGAAGCTCCGTCCCGCCCCGCGGGCCGGCTCCGCCCTCACCTCCCGGCCGCGGCTGC  
CCTCTGCCCCGGGTTGTCCAAGATGGAGGGCGCTCCACCGGGGTGCTCGCCCTCCGGCTC  
CTGCTGTTCTGTGGCGCTACCCGCCTCCGGCTGGCTGACGACGGGCGCCCCCGAGCCGCCG  
CCGCTGTCCGGAGCCCCACAGGACGGCATCAGAATTAATGTAACTACACTGAAAGATGAT  
GGGGACATATCTAAACAGCAGGTTGTTCTTAACATAACCTATGAGAGTGGACAGGTGTAT  
GTAAATGACTTACCTGTAAATAGTGGTGTAAACCCGAATAAGCTGTCAGACTTTGATAGTG  
AAGAATGAAAATCTTGAAAATTTGGAGGAAAAAGAATATTTTGGAATTGTCAGTGTAAGG  
ATTTTAGTTTCATGAGTGGCCTATGACATCTGGTTCCAGTTTGCAACTAATTGTCATTCAA  
GAAGAGGTAGTAGAGATTGATGGAAAACAAGTTTCAAGCAAAAGGATGTCAGTCAAATTGAT  
ATTTTAGTTAAGAACCGGGGAGTACTCAGACATTCAAACCTATACCCCTCCCTTTGGAAGAA  
AGCATGCTCTACTCTATTTCTCGAGACAGTGACATTTTATTTACCCTTCCTAACCTCTCC  
AAAAAAGAAAGTGTTAGTTCACTGCAAACCACTAGCCAGTATCTTATCAGGAATGTGGAA  
ACCACTGTAGATGAAGATGTTTTACCTGGCAAGTTACCTGAAACTCCTCTCAGAGCAGAG  
CCGCCATCTTCATATAAGGTAATGTGTGTCAGTGGATGGAAAAGTTTAGAAAAGATCTGTGT  
AGGTTCTGGAGCAACGTTTTCCAGTATTCTTTTCAGTTTTTGAACATCATGGTGGTTGGA  
ATTACAGGAGCAGCTGTGGTAATAACCATCTTAAGGTGTTTTTCCAGTTTCTGAATAC  
AAAGGAATTCCTCAGTTGGATAAAGTGGACGTCATACCTGTGACAGCTATCAACTTATAT  
CCAGATGGTCCAGAGAAAAGAGCTGAAAACCTTGAAGATAAAACATGTATTTAAAACGCC  
ATCTCATATCATGGACTCCGAAGTAGCCTGTTGCCTCAAATTTGCCACTTGAATATAAT  
TTTCTTTAAATCGTT

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**FIGURE 178**

MEGAPPGSLALRLLLFVALPASGWLTGAPPEPPPLSGAPQDGIRINVTTLKDDGDISKQQ  
VVLNITYESGQVYVNDLPVNSGVTRISCQTLIVKNENLENLEEKEYFGIVSVRILVHEWP  
MTSGSSLQLIVIQEEVVEIDGKQVQQKDVTEIDILVKNRGVLRHSNYTLPLEESMLYSIS  
RDS DILFTLPNLSKKESVSSLQTTSQYLIRNVETTVDVLPGLPETPLRAEPPSSYKV  
MCQWMEKFRKDL CRFWSNVFPVFFQFLNIMVVGITGA AVVITILKVFFPVSEYKGILQLD  
KVDVIPVTAINLYPDGPEKRAENLEDKTCI

**Signal peptide:**

1-23

**Transmembrane domain:**

266-284

**Leucine zipper pattern:**

155-177

**N-glycosylation site:**

46-50, 64-68, 166-170, 191-195

**Motif name: N-myristoylation site:**

3-9, 42-48, 273-279

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**FIGURE 179**

CTCCTTAGGTGGAAACCTGGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATAC  
GTCCCCGGGCAGGGGTGACAACAGGTGTCATCTTTTTTGATCTCGTGTGTGGCTGCCTTCC  
TATTTCAAGGAAAGACGCCAAGGTAATTTTGACCCAGAGGAGCAATGATGTAGCCACCTC  
CTAACCTTCCCTTCTTGAACCCCCAGTTATGCCAGGATTTACTAGAGAGTGTCAACTCAA  
CCAGCAAGCGGCTCCTTCGGCTTAACCTGTGGTTGGAGGAGAGAACCTTTGTGGGGCTGC  
GTTCTCTTAGCAGTGCTCAGAAGTGACTTGCCTGAGGGTGGACCAGAAGAAAGGAAAGGT  
CCCCTCTTGCTGTTGGCTGCACATCAGGAAGGCTGTGATGGGAATGAAGGTGAAAACCTTG  
GAGATTTCACTTCAGTCATTGCTTCTGCCTGCAAGATCATCCTTTAAAAGTAGAGAAGCT  
GCTCTGTGTGGTGGTTAACTCCAAGAGGCAGAACTCGTTCTAGAAGGAAATGGATGCAAG  
CAGCTCCGGGGGGCCCCAAACGCATGCTTCTGTGGTCTAGCCCAGGGAAGCCCTTCCGTG  
GGGGCCCCGGCTTTGAGGGATGCCACCGGTTCTGGACGCATGGCTGATTCTGAATGATG  
ATGGTTTCGCCGGGGGCTGCTTGCCTGGATTTCGCCGGTGGTGGTTTTGCTGGTGTCTCTC  
TGCTGTGCTATCTCTGTCTGTACATGTTGGCCTGCACCCCCAAAAGGTGACGAGGAGCAG  
CTGGCACTGCCCAGGGCCAACAGCCCCACGGGGAAGGAGGGGTACCAGGCCGTCTTTCAG  
GAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGCGGCAGATCGCACAGCTC  
AAGGAGGAGCTGCAGGAGAGGAGTGAGCAGCTCAGGAATGGGCAGTACCAAGCCAGCGAT  
GCTGCTGGCCTGGGTCTGGACAGGAGCCCCCAGAGAAAACCCAGGCCGACCTCCTGGCC  
TTCCTGCACTCGCAGGTGGACAAGGCAGAGGTGAATGCTGGCGTCAAGCTGGCCACAGAG  
TATGCAGCAGTGCCTTTCGATAGCTTTACTCTACAGAAGGTGTACCAGCTGGAGACTGGC  
CTTACCCGCCACCCCGAGGAGAAGCCTGTGAGGAAGGACAAGCGGGATGAGTTGGTGGAA  
GCCATTGAATCAGCCTTGGAGACCCTGAACAATCCTGCAGAGAACAGCCCCAATCACCGT  
CCTTACACGGCCTCTGATTTTCATAGAAGGGATCTACCGAACAGAAAGGGACAAAGGGACA  
TTGTATGAGCTCACCTTCAAAGGGGACCACAAACACGAATTCAAACGGCTCATCTTATTT  
CGACCATTTCAGCCCCATCATGAAAAGTGAAAAATGAAAAGCTCAACATGGCCAACACGCTT  
ATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGGACAAGTTCCGGCAGTTCATGCAGAAT  
TTCAGGGAGATGTGCATTGAGCAGGATGGGAGAGTCCATCTCACTGTTGTTTACTTTGGG  
AAAGAAGAAATAAATGAAGTCAAAGGAATACTTGAAAACACTTCCAAAGCTGCCAATTTC  
AGGAACTTTACCTTCATCCAGCTGAATGGAGAATTTTCTCGGGGAAGGGACTTGATGTT  
GGAGCCCGCTTCTGGAAGGGAAGCAACGTCTTCTCTTTTTCTGTGATGTGGACATCTAC  
TTCACATCTGAATTCCTCAATACGTGTAGGCTGAATACACAGCCAGGGAAGAAGGTATTT  
TATCCAGTTCCTTTTCAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTC  
CCTCCCTTGGAACAGCAGCTGGTCATAAAGAAGGAACTGGATTTTGGAGAGACTTTGGA  
TTTGGGATGACGTGTGAGTATCGGTGAGACTTCATCAATATAGGTGGGTTTGATCTGGAC  
ATCAAAGGCTGGGGCGGAGAGGATGTGCACCTTTATCGCAAGTATCTCCACAGCAACCTC  
ATAGTGGTACGGACGCCTGTGCGAGGACTCTTCCACCTCTGGCATGAGAAGCGCTGCATG  
GACGAGCTGACCCCCGAGCAGTACAAGATGTGCATGCAGTCCAAGGCCATGAACGAGGCA  
TCCCACGGCCAGCTGGGCATGCTGGTGTTCAGGCACGAGATAGAGGCTCACCTTCGAAA  
CAGAAACAGAAGACAAGTAGCAAAAAACATGAACTCCAGAGAAGGATTGTGGGAGACA  
CTTTTTCTTCTTTTGAATTAAGTGGCTGCAACAGAGAAAAGACTTCCATAAA  
GGACGACAAAAGAATTGGACTGATGGGTGAGAGATGAGAAAGCCTCCGATTTCTCTCTGT  
TGGGCTTTTTTACAACAGAAATCAAAATCTCCGCTTTGCCTGCAAAAGTAACCCAGTTGCA  
CCCTGTGAAGTGTCTGACAAAGGCAGAAATGCTTGTGAGATTATAAGCCTAATGGTGTGGA  
GGTTTTGATGGTGTTTACAATACACTGAGACCTGTTGTTTTGTGTGCTCATTGAAATATT  
CATGATTTAAGAGCAGTTTTGTAAAAAATTCATTAGCATGAAAGGCAAGCATATTTCTCC  
TCATATGAATGAGCCTATCAGCAGGGCTCTAGTTTCTAGGAATGCTAAAAATATCAGAAGG  
CAGGAGAGGAGATAGGCTTATTATGATACTAGTGAGTACATTAAGTAAAAATAAATGGAC  
CAGAAAAGAAAAGAAACCATAAATATCGTGTATATTTTCCCCAAGATTAACCAAAAATA

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ATCTGCTTATCTTTTTGGTTGTCCTTTTAACTGTCTCCGTTTTTTTTCTTTTATTTAAAAA  
TGCACTTTTTTTCCCTTGTGAGTTATAGTCTGCTTATTTAATTACCACTTTGCAAGCCTT  
ACAAGAGAGCACAAAGTTGGCCTACATTTTTTATATTTTTTAAGAAGATACTTTGAGATGCA  
TTATGAGAACTTTCAGTTCAAAGCATCAAATTGATGCCATATCCAAGGACATGCCAAATG  
CTGATTCTGTCAGGCACTGAATGTCAGGCATTGAGACATAGGGAAGGAATGGTTTGTACT  
AATACAGACGTACAGATACTTTCTCTGAAGAGTATTTTCGAAGAGGAGCAACTGAACACT  
GGAGGAAAAGAAAATGACACTTTCTGCTTTACAGAAAAGGAACTCATTGAGACTGGTGA  
TATCGTGATGTACCTAAAAGTCAGAAACCACATTTTCTCCTCAGAAGTAGGGACCGCTTT  
CTTACCTGTTTAAATAAACCAAAGTATACCGTGTGAACCAAACAATCTCTTTTCAAAACA  
GGGTGCTCCTCCTGGCTTCTGGCTTCCATAAGAAGAAATGGAGAAAAATATATATATATA  
TATATATATTGTGAAAGATCAATCCATCTGCCAGAATCTAGTGGGATGGAAGTTTTTGCT  
ACATGTTATCCACCCAGGCCAGGTGGAAGTAACTGAATTATTTTTTAAATTAAGCAGTT  
CTACTCAATCACCAAGATGCTTCTGAAAATTGCATTTTATTACCATTTCAAACATTTTTT  
TAAAAATAAATACAGTTAACATAGAGTGGTTTCTTCATTGATGTGAAAATTATTAGCCAG  
CACCAGATGCATGAGCTAATTATCTCTTTGAGTCCTTGCTTCTGTTTGCTCACAGTAAAC  
TCATTGTTTAAAAGCTTCAAGAACATTCAAGCTGTTGGTGTGTTAAAAAATGCATTGTAT  
TGATTTGTTACTGGTAGTTTATGAAATTTAATTAAACACAGGCCATGAATGGAAGGTGGT  
ATTGCACAGCTAATAAAATATGATTTGTGGATATGAA

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**FIGURE 180**

MMVRRGLLAWISRVVLLVLLCCAISVLYMLACTPKGDEEQLALPRANSPTGKEGYQAV  
LQEWEEQHRNYVSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADL  
LAFLHSQVDKAEVNAGVKLATEYA AVPFDSFTLQKVYQLETGLTRHPPEKPVRKDKRDEL  
VEAIESALETLNPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLI  
LFRPFSPIMKVKNEKLNMAN TLINVIVPLAKRVDKFRQFMQNFREMCI EQDGRVHLTVVY  
FGKEEINEVKGILENTSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVD  
IYFTSEFLNTCRLNTQPGKKVFYPVLF SQYNPGIIYGHHD AVPPLEQQLV IKKETGFWRD  
FGFGMTCQYRSDFINIGGFDLDIKGWGGEDVHLYRKYLHSNLIVVRTPV RGLFHLWHEKR  
CMDELTPEQYKMC MQSKAMNEASHGQLGMLVFRHEIEAHLRKQKQKTSSKKT

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**FIGURE 181**

CGTCTCTGCGTTTCGCCATGCGTCCCGGGGCGCCAGGGCCACTCTGGCCTCTGCCCTGGGG  
GGCCCTGGCTTGGGCCGTGGGCTTCGTGAGCTCCATGGGCTCGGGGAACCCCGCGCCCGG  
TGGTGT'TTGCTGGCTCCAGCAGGGCCAGGAGGCCACCTGCAGCCTGGTGCTCCAGACTGA  
TGTCACCCGGGCCGAGTGCTGTGCCTCCGGCAACATTGACACCGCCTGGTCCAACCTCAC  
CCACCCGGGGAAACAAGATCAACCTCCTCGGCTTCTTGGGCCTTGTCACCTGCCTTCCCTG  
CAAAGATTTCGTGCGACGGCGTGAGTGCGGCCCGGGCAAGGCGTGCCGCATGCTGGGGGG  
CCGCCCGCGCTGCGAGTGCGCGCCCGACTGCTCGGGGCTCCCGGCGCGGCTGCAGGTCTG  
CGGCTCAGACGGCGCCACCTACCGCGACGAGTGCGAGCTGCGCGCCGCGCGCTGCCGCGG  
CCACCCGGACCTGAGCGTCATGTACCGGGGCCGCTGCCGCAAGTCCTGTGAGCACGTGGT  
GTGCCCGCGGCCACAGTCGTGCGTCTGTGGACCAGACGGGCAGCGCCCACTGCGTGGTGTG  
TCGAGCGGCGCCCTGCCCTGTGCCCTCCAGCCCCGGCCAGGAGCTTTGCGGCAACAACAA  
CGTCACCTACATCTCCTCGTGCCACATGCGCCAGGCCACCTGCTTCTGGGCCGCTCCAT  
CGGCGTGCGCCACGCGGGCAGCTGCGCAGGCACCCCTGAGGAGCCGCCAGGTGGTGAGTC  
TGCAGAAGAGGAAGAGAACTTCGTGTGAGCCTGCAGGACAGGCCTGGGCCTGGTGCCCGA  
GGCCCCCATCATCCCCCTGTTATTTATTGCCACAGCAGAGTCTAATTTATATGCCACGGA  
CACTCCTTAGAGCCCGGATTTCGGACCACTTGGGGATCCCAGAACCTCCCTGACGATATCC  
TGGAAGGACTGAGGAAGGGAGGCCTGGGGGCCGGCTGGTGGGTGGGATAGACCTGCGTTC  
CGGACACTGAGCGCCTGATTTAGGGCCCTTCTCTAGGATGCCCCAGCCCCCTACCCTAAGA  
CCTATTGCCGGGGAGGATTCCACACTTCCGCTCCTTTGGGGATAAACCTATTAATTATTG  
CTACTATCAAGAGGGGCTGGGCATTCTCTGCTGGTAATTCTGAAGAGGCATGACTGCTTT  
TCTCAGCCCCAAGCCTCTAGTCTGGGTGTGTACGGAGGGTCTAGCCTGGGTGTGTACGGA  
GGGTCTAGCCTGGGTGAGTACGGAGGGTCTAGCCTGGGTGAGTACGGAGGGTCTAGCCTG  
GGTGAGTACGGAGGGTCTAGCCTGGGTGTGTATGGAGGATCTAGCCTGGGTGAGTATGGA  
GGGTCTAGCCTGGGTGAGTATGGAGGGTCTAGCCTGGGTGTGTATGGAGGGTCTAGCCTG  
GGTGAGTATGGAGGGTCTAGCCTGGGTGTGTATGGAGGGTCTAGCCTGGGTGAGTATGGA  
GGGTCTAGCCTGGGTGTGTACGGAGGGTCTAGTCTGAGTGCGTGTGGGGACCTCAGAACA  
CTGTGACCTTAGCCCAGCAAGCCAGGCCCTTCATGAAGGCCAAGAAGGCTGCCACCATTCT  
CCTGCCAGCCCAAGAACTCCAGCTTCCCCACTGCCTCTGTGTGCCCCCTTTGCGTCCTGTG  
AAGGCCATTGAGAAATGCCAGTGTGCCCCCTGGGAAAGGGCACGGCCTGTGCTCCTGAC  
ACGGGCTGTGCTTGGCCACAGAACCACCCAGCGTCTCCCCTGCTGCTGTCCACGTCAGTT  
CATGAGGCAACGTCGCGTGGTCTCAGACGTGGAGCAGCCAGCGGCAGCTCAGAGCAGGGC  
ACTGTGTCCGGCGGAGCCCAAGTCCACTCTGGGGGAGCTCTGGCGGGGACCACGGGCCACT  
GCTCACCCACTGGCCCCGAGGGGGGTGTAGACGCCAAGACTCACGCATGTGTGACATCCG  
GAGTCCTGGAGCCGGGTGTCCCAGTGGCACCCTAGGTGCCTGCTGCCTCCACAGTGGGG  
TTCACACCCAGGGCTCCTTGGTCCCCACAACCTGCCCCGGCCAGGCCTGCAGACCCAGA  
CTCCAGCCAGACCTGCCTCACCCACCAATGCAGCCGGGGCTGGCGACACCAGCCAGGTGC  
TGGTCTTGGGCCAGTTCTCCCACGACGGCTCACCCCTCCCCTCCATCTGCGTTGATGCTCA  
GAATCGCCTACCTGTGCCTGCGTGTAACCCACAGCCTCAGACCAGCTATGGGGAGAGGAC  
AACACGGAGGATATCCAGCTTCCCCGGTCTGGGGTGAGGAATGTGGGGAGCTTGGGCATC  
CTCCTCCAGCCTCCTCCAGCCCCCAGGCAGTGCCCTTACCTGTGGTGCCAGAAAAGTGCC  
CCTAGGTTGGTGGGTCTACAGGAGCCTCAGCCAGGCAGCCACCCACCCCTGGGGCCCTG  
CCTCACCAAGGAAATAAAGACTCAAGCCATAAAAAAA

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**FIGURE 182**

MRPGAPGPLWPLPWGALAWAVGVSSMSGGNPAPGGVCWLQQGQEATCSLVLQTDVTRAE  
CCASGNIDTAWSNLTHPGNKINLLGFLGLVHCLPCKDSCDGVECGPGKACRMLGGRPRCE  
CAPDCSGLPARLQVCGSDGATYRDECELRAARCRGHPDLSVMYRGRCRKSCHEVVCPRPQ  
SCVVDQTGSAHCVVCRAAPCPVPSSPGQELCGNNNVITYISSCHMRQATCFLGRSIGVRHA  
GSCAGTPEEPPGGESAEEEEENFV

**Important features:****Signal peptide:**

amino acids 1-20

**N-glycosylation sites:**

amino acids 73-77, 215-219

**Osteonectin domain proteins:**

amino acids 97-130, 169-202



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**FIGURE 183**

CACTCATTTCATTCCAAAGGGTCTCTCAAGGCAATGGTAATGTGCAAGGAGGTGATACCTA  
AATGAATGACCAAAAGAACATGCTTCTGCTTTTGTGTGTCTCCTACATTTTAGACATTTG  
TTTGTTTTCTCTTGGTAGCCTTTAAATTCCTTGAAGCCCAGGACCATGTCTCACTTACCTT  
TGTGTTTTCCACTAACTAGTCTACCTCCTGGAATTGGCAGATACTCAGTGAAAGCCTGTGA  
AATAAGTGATGTCTATTTCTAGCATATTATTCTGAGATTTAATGATAGATTTAGTGATTG  
AATGAGATTTCCATTTTCAAATACAGCAAAAGCATAACTATTTTCATTCATTTCATATTCA  
TTCAACTTCATTCTCAAATTAGGTCCTGAGTTAACTAATAATTACCTTTGAAATGTGTG  
GGTTATTTGAGGCAATCAGGTGGTGACATTGAGCTCTCAGCCAGAGTTTGTCTGGAAT  
TGATTCAGTTCATTTGCATTGATTTTGTCTCAGAAGCCAAGGTTTCCCATGAAAAATC  
ATTTCCCACTTGAATTGGGCTGTGATTCTTGCTGCGTTTAAGTAAAGGAAGCCTCTTGGTT  
CTAGTTCTGCAAACTTACACACTGAACTGGGACAAGTTTTTGTCTTAGAGTAATGGCTGGG  
AAAAGAGGAACCTTTCATTTTATTTCAGAAGTCAAAAACAAAGGCCTCCAGCCACCTGGA  
GATGTTTTGTGTCAGACACCAGCCTGGCTCTGTCTTTATGCCTAACAATTGAGCATCCAG  
TCTTCTTTGTGCTGGGACCATTGCTCAGCTCTGCAAGGGGAAAAGAGGGAGAAAGCCAGA  
GCTGCCAGGCTTCTTGCACTGGGGCCGGGGAGGGTTCTTGGGAAGCAGGTGCTCTCTGG  
CTTCTTGGTACGTGAGGCTCTCGGAGCTGCCTCTCCTCTGACCCTCAGGTCCTCACCGAG  
TTTGCTCCAGGAGTATATTGAAAACATACCCAGTGCTCTCTCAAGCACCCACTGCTTAGA  
GGGCCCAGATTTCTTTTCTTCTTCCCTTGCAAGCTGGAGACTGCATCGGGCATCTGG  
TGTTTAAACTAAACAGGAAAACCTGACTAAAGGTCCACAGTGCTCATTGTGTAGACTAGCT  
GCCCTCCGATGGGTGCTCTGATTATCAGTGGTTCCAGTGCAAGGCCTGTCACTAAACAGG  
CCTCACTTCCTCCTTGGGGGCTTTCCCATGGGAGGTGTGGCTTTTTACTCTACATGGAAA  
TGACTCTCTGCAGCCACAGAACACAGTCATTTTCTGAATTATCCAGTCTCTCATGCGCC  
CTGGATTCTCCTCAGATGCCTTATATCTCTTGTGCAAAGTTGTCTAAATTTGGTTCCCAG  
CTTCCAAGCCTTGCCTTTTGGCCTTCTGGAAGTATTTTTGTTGATGAGTCGTCTGTCTAT  
TATTCTCTAAATGATTTGCTTTTTGTTTCTTTCATTTCCTATTTCCACCCACATATACA  
CACATGCTTCTTAACTTAGGGGATTACATGCCAATAAATCTATTGTTGAAAATGCACTAA  
TACTATCGCAAAGACGAAAATTCACAGGCTGAACCGTTGTAAGTCCATATGCTCCTCAAC  
TTACATGTGTGATGGAGTTATGCCCAAATAAGTCCATCGTCAAGTTGAAAAATCAAAATC  
AAGCCATCTTAGGTTGAGGACCATTGTGTTGTACCTCAAAGATGTCATATCTTTAAACA  
TACTCCCTAGCTTTTCTTTTACTTTTTATTTTGAAGTAATTATAGAATCACAGAAAGTT  
GCAAAAAA

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**FIGURE 184**

MGALIIISGSSAGPVTQASLPPWGLSHGRCGFLLYMENTLCSHRTQSFSELSQSLMRPGF  
LQMPYISCAKLSKIWFPAKPCLLAFLEVFLLMSRLSLFSKMICFLFLSFLFPPHIYTHAS

**Important features of the protein:**

**Signal peptide:**

amino acids 1-41

**Transmembrane domain:**

amino acids 88-107

**Casein kinase II phosphorylation site:**

amino acids 47-50

**N-myristoylation site:**

amino acids 24-29

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**FIGURE 185**

AACTCAAACCTCCTCTCTCTGGGAAAACGCGGTGCTTGCTCCTCCCGGAGTGGCCTTGGCA  
GGGTGTTGGAGCCCTCGGTCTGCCCCGTCCGGTCTCTGGGGCCAAGGCTGGGTTTCCCTC  
ATGTATGGCAAGAGCTCTACTCGTGCGGTGCTTCTTCTCCTTGGCATAACAGCTCACAGCT  
CTTTGGCCTATAGCAGCTGTGGAAATTTATACCTCCCGGGTGCTGGAGGCTGTAAATGGG  
ACAGATGCTCGGTTAAAATGCACCTTTCTCCAGCTTTGCCCCCTGTGGGTGATGCTCTAACA  
GTGACCTGGAATTTTTCGTCTCTAGACGGGGGACCTGAGCAGTTTGTATTCTACTACCAC  
ATAGATCCCTTCCAACCCATGAGTGGGCGGTTTAAGGACCGGGTGTCTTGGGATGGGAAT  
CCTGAGCGGTACGATGCCTCCATCCTTCTCTGGAACTGCAGTTCGACGACAATGGGACA  
TACACCTGCCAGGTGAAGAACCCACCTGATGTTGATGGGGTGATAGGGGAGATCCGGCTC  
AGCGTCGTGCACACTGTACGCTTCTCTGAGATCCACTTCCTGGCTCTGGCCATTGGCTCT  
GCCTGTGCACTGATGATCATAATAGTAATTGTAGTGGTCCTCTTCCAGCATTACCGGAAA  
AAGCGATGGGCCGAAAGAGCTCATAAAGTGGTGGAGATAAAATCAAAAGAAGAGGAAAGG  
CTCAACCAAGAGAAAAAGGTCTCTGTTTATTTAGAAGACACAGACTAA~~CA~~CAATTTTAGATG  
GAAGCTGAGATGATTTCCAAGAACAAGAACCCTAGTATTTCTTGAAGTTAATGGAACTT  
TTCTTTGGCTTTTCCAGTTGTGACCCGTTTTCCAACCAGTTCTGCAGCATATTAGATTCT  
AGACAAGCAACACCCCTCTGGAGCCAGCACAGTGCTCCTCCATATCACCAGTCATACACA  
GCCTCATTATTAAGGTCTTATTTAATTTTCAAGAGTGTAATTTTTTCAAGTGCTCATTAGG  
TTTTATAACAAGAAGCTACATTTTTTGCCCTTAAGACACTACTTACAGTGTTATGACTTG  
TATACACATATATTGGTATCAAAGGGGATAAAAGCCAATTTGTCTGTTACATTTCTTTTC  
ACGTATTTCTTTTAGCAGCACTTCTGCTACTAAAGTTAATGTGTTTACTCTCTTTCTTC  
CCACATTCTCAATTTAAAGGTGAGCTAAGCCTCCTCGGTGTTTCTGATTAAACAGTAAATC  
CTAAATTCAAACCTGTTAAATGACATTTTTATTTTTATGTCTCTCCTTAACATATGAGACAC  
ATCTTGTTTTACTGAATTTCTTTCAATATTCCAGGTGATAGATTTTTGTGTCG

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**FIGURE 186**

MYGKSSTRAVLLLLGIQLTALWPAAVEIYTSRVLEAVNGTDARLKCTFSSFAPVGDALT  
VTWNFRPLDGGPEQFVFYHIDPFQPMSEGRFKDRVSWDGNPERYDASILLWKLQFDDNGT  
YTCQVKNPPDVGVIIEIRLSVVHTVRFSEIHFLALALIGSACALMIIIVIVVVLFFQHYRK  
KRWAEARAHKVVEIKSKEEERLNQEKVSVYLETD

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**FIGURE 187**

GCATTTTTGTCTGTGCTCCCTGATCTTCAGGTCACCACCATGAAGTTCTTAGCAGTCCTG  
GTACTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCAGAATCCGACAACAGCTGCTCCA  
GCTGACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAAACCACT  
GCTGCTGCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCTACC  
ACTGCTCGTAAAGACATTCCAGTTTTACCCAAATGGGTGGGGATCTCCCGAATGGTAGA  
GTGTGTCCCTGAGATGGAATCAGCTTGAGTCTTCTGCAATTGGTCACAACCTATTCATGCT  
TCCTGTGATTTTCATCCAACCTACTTACCTTGCCTACGATATCCCCTTTATCTCTAATCAGT  
TTATTTTCTTTCAAATAAAAAATAACTATGAGCAACATAAAAAAAAAAAAAA

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## FIGURE 188

MKFLAVLVLLGVSI FLVSAQNPTTAAPADTYPATGPADDEAPDAETTAAATTATTAAPT  
ATTAASTTARKDIPVLPKWVGDL PNGRVCP

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**FIGURE 189**

GAGCGAACATGGCAGCGGTTGGCGGTTTTGGTGTGTCTCTGTGACCATGGTGGTGGCGC  
TGCTCATCGTTTTGCGACGTTCCCTCAGCCTCTGCCCAAAGAAAGAAGGAGATGGTGTAT  
CTGAAAAGGTTAGTCAGCTGATGGAATGGACTAACAAAAGACCTGTAATAAGAATGAATG  
GAGACAAGTTCGGTCGCCTTGTGAAAGCCCCACCGAGAAATTACTCCGTTATCGTCATGT  
TCACTGCTCTCCAAGTGCATAGACAGTGTGTGCTTTGCAAGCAAGCTGATGAAGAATTCC  
AGATCCTGGCAAACCTCTGGCGATACTCCAGTGCATTACCAACAGGATATTTTTTGGCCA  
TGGTGGATTTTGATGAAGGCTCTGATGTATTTTCAAGTGTAAACATGAATTCAGCTCCAA  
CTTTCATCAACTTTCTGCAAAAGGGAAACCCAAACGGGGTGATACATATGAGTTACAGG  
TGCGGGGTTTTTTCAGCTGAGCAGATTGCCCGGTGGATCGCCGACAGAACTGATGTCAATA  
TTAGAGTGATTAGACCCCCAAATTATGCTGGTCCCTTATGTTGGGATTGCTTTTGGCTG  
TTATTGGTGGACTTGTGTATCTTCGAAGAAGTAATATGGAATTTCTCTTAATAAACTG  
GATGGGCTTTTTCAGCTTTGTGTTTTGTGCTTGCTATGACATCTGGTCAAATGTGGAACC  
ATATAAGAGGACCACCATATGCCATAAGAATCCCCACACGGGACATGTGAATTATATCC  
ATGGAAGCAGTCAAGCCCAGTTTGTAGCTGAAACACACATTGTTCTTCTGTTTAATGGTG  
GAGTTACCTTAGGAATGGTGCCTTTTATGTGAAGCTGCTACCTCTGACATGGATATTGGAA  
AGCGAAAGATAATGTGTGTGGCTGGTATTGGACTTGTGTATTATTCTTCAGTTGGATGC  
TCTCTATTTTTAGATCTAAATATCATGGCTACCCATACAGCTTTCTGATGAGTTAAAAAG  
GTCCCAGAGATATATAGACACTGGAGTACTGGAAATTGAAAAACGAAAATCGTGTGTGTT  
TGAAAAGAAGAATGCAACTTGTATATTTTTGTATTACCTCTTTTTTTTCAAGTGATTTAAAT  
AGTTAATCATTTAAACCAAAGAAGATGTGTAGTGCCTTAACAAGCAATCCTCTGTCAAAAT  
CTGAGGTATTTGAAAATAATTATCCTCTTAACCTTCTCTTCCCAGTGAACTTTATGGAAC  
ATTTAATTTAGTACAATTAAAGTATATTATAAAAAATTGTAAACTACTACTTTGTTTTAGT  
TAGAACAAAGCTCAAAACTACTTTAGTTAACTTGGTTCATCTGATTTTATATTGCCCTTATC  
CAAAGATGGGGAAAGTAAGTCCCTGACCAGGTGTTCCACATATGCCTGTTACAGATAACT  
ACATTAGGAATTCATTCTTAGCTTCTTCATCTTTGTGTGGATGTGTATACTTTACGCATC  
TTTCCTTTTGTAGTAGAGAAATTATGTGTGTGTCATGTGGTCTTCTGAAAATGGAACACCATT  
CTTCAGAGCACACGTCTAGCCCTCAGCAAGACAGTTGTTTCTCCTCCTCCTTGCATATTT  
CCTACTGCGCTCCAGCCTGAGTGATAGAGTGAGACTCTGTCTCAAAAAAAGTATCTCTA  
AATACAGGATTATAATTTCTGCTTGAGTATGGTGTAACTACCTTGTATTTAGAAAGATT  
TCAGATTCAATCCATCTCCTTAGTTTTCTTTTAAGGTGACCCATCTGTGATAAAAATATA  
GCTTAGTGCTAAAATCAGTGTAACCTTATACATGGCCTAAAATGTTTCTACAAATTAGAGT  
TTGTCACTTATTTCCATTTGTACCTAAGAGAAAAATAGGCTCAGTTAGAAAAGGACTCCCT  
GGCCAGGCGCAGTGACTTACGCCTGTAATCTCAGCACTTTGGGAGGCCAAGGCAGGCAGA  
TCACGAGGTCAGGAGTTTCGAGACCATCCTGGCCAACATGGTGAAACCCCGTCTCTACTAA  
AAATATAAAAAATTAGCTGGGTGTGGTGGCAGGAGCCTGTAATCCCAGCTACACAGGAGGC  
TGAGGCACGAGAATCACTTGAACCTCAGGAGATGGAGGTTTCAGTGAGCCGAGATCACGCC  
ACTGCACTCCAGCCTGGCAACAGAGCGAGACTCCATCTCAAAAAAAAAAAAAA

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**FIGURE 190**

MAARWRFWCVSVTMVVALLIVCDVPSASAQRKKEMVLSEKVSQLMWETNKRFPVIRMNGDK  
FRRLVKAPPRNYSVIVMFTALQLHRQCVVCKQADEEFQILANSWRYSSAFTNRIFFAMVD  
FDEGSDVFQMLNMNSAPTFINFPAGKPKRGDTYELQVRGFSAEQIARWIADRTDVNIRV  
IRPPNYAGPLMLGLLLLAVIGGLVYLRRSNMEFLFNKTGWAFALCFVLAMTSGQMWNHIR  
GPPYAHKNPHTGHVNYIHGSSQAQFVAETHIVLLFNNGGVTLGMVLLCEAATSDMDIGKRK  
IMCVAGIGLVVLFFSWMLSIFRSKYHGYPSFLMS

**Signal peptide:**

amino acids 1-29

**Transmembrane domains:**

amino acids 183-205, 217-237, 217-287, 301-321



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**FIGURE 191**

GAGAGAAAGTCAGCCTGGCAGAGAGACTCTGAAATGAGGGATTAGAGGTGTTCAAGGAGCA  
AGAGCTTCAGCCTGAAGACAAGGGAGCAGTCCCTGAAGACGCTTCTACTGAGAGGTCTGC  
CATGGCCTCTCTTGGCCTCCAACTTGTGGGCTACATCCTAGGCCTTCTGGGGCTTTTGGG  
CACACTGGTTGCCATGCTGCTCCCCAGCTGGAACAAGTTCTTATGTCGGTGCCAGCAT  
TGTGACAGCAGTTGGCTTCTCCAAGGGCCTCTGGATGGAATGTGCCACACACAGCACAGG  
CATCACCCAGTGTGACATCTATAGCACCCTTCTGGGCCTGCCGCTGACATCCAGGCTGC  
CCAGGCCATGATGGTGACATCCAGTGCAATCTCCTCCCTGGCCTGCATTATCTCTGTGGT  
GGGCATGAGATGCACAGTCTTCTGCCAGGAATCCCGAGCCAAAGACAGAGTGGCGGTAGC  
AGGTGGAGTCTTTTTTCATCCTTGGAGGCCTCCTGGGATTCATTCCTGTTGCCTGGAATCT  
TCATGGGATCCTACGGGACTTCTACTCACCCTGGTGCCTGACAGCATGAAATTTGAGAT  
TGGAGAGGCTCTTTACTTGGGCATTATTTCTTCCCTGTTCTCCCTGATAGCTGGAATCAT  
CCTCTGCTTTTCTGCTCATCCCAGAGAAATCGCTCCAATACTACGATGCCTACCAAGC  
CCAACCTCTTGCCACAAGGAGCTCTCCAAGGCCTGGTCAACCTCCCAAAGTCAAGAGTGA  
GTTCAATTCTACAGCCTGACAGGGTATGTGTGAAAGAACCAGGGGCCAGAGCTGGGGGGT  
GGCTGGGTCTGTGAAAAACAGTGGACAGCACCCCGAGGGCCACAGGTGAGGGACACTACC  
ACTGGATCGTGTGAGAAGGTGCTGCTGAGGATAGACTGACTTTGGCCATTGGATTGAGCA  
AAGGCAGAAATGGGGGCTAGTGTAACAGCATGCAGGTTGAATTGCCAAGGATGCTCGCCA  
TGCCAGCCTTTCTGTTTTCTCACCTTGCTGCTCCCCTGCCCTAAGTCCCCAACCTCAA  
CTTGAAACCCCATTCCTTAAGCCAGGACTCAGAGGATCCCTTTGCCCTCTGGTTTACCT  
GGGACTCCATCCCCAAACCCACTAATCACATCCCCTGACTGACCCTCTGTGATCAAAGA  
CCCTCTCTCTGGCTGAGGTTGGCTCTTAGCTCATTGCTGGGGATGGGAAGGAGAAGCAGT  
GGCTTTTGTGGGCATTGCTCTAACCTACTTCTCAAGCTTCCCTCCAAAGAACTGATTGG  
CCCTGGAACCTCCATCCCCTCTTGTTATGACTCCACAGTGTCCAGACTAATTTGTGCAT  
GAACTGAAATAAAACCATCCTACGGTATCCAGGGAACAGAAAGCAGGATGCAGGATGGGA  
GGACAGGAAGGCAGCCTGGGACATTTAAAAAATA

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**FIGURE 192**

MASLGLQLVG YILG LLLG LTLVAMLLPSWKTSSYVGASIVTAVGFSKGLWMECATHSTG  
ITQCDIYSTLLGLPADIQAAQAMMVTSSAIISSLACIISVVGMRCTVFCQESRAKDRVAVA  
GGVFFILG LLLGFIPVAWNLHGILRDFYSPLVPDSMKFEIGEALYLGIISSLFSLIAGII  
LCFSCSSQRNRSNYYDAYQAQPLATRSSPRPGQPPKVKSEFN SYSLTGYV

**Important features of the protein:**

**Signal peptide:**

amino acids 1-24

**Transmembrane domains:**

amino acids 82-102, 117-140, 163-182

**N-glycosylation site:**

amino acids 190-193

**PMP-22 / EMP / MP20 family proteins:**

amino acids 46-59

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**FIGURE 193**

CTCCACTGCAACCACCCAGAGCCATGGCTCCCCGAGGCTGCATCGTAGCTGTCTTTGCCA  
TTTTCTGCATCTCCAGGCTCCTCTGCTCACACGGAGCCCCAGTGGCCCCCATGACTCCTT  
ACCTGATGCTGTGCCAGCCACACAAGAGATGTGGGGACAAGTTCTACGACCCCCTGCAGC  
ACTGTTGCTATGATGATGCCGTCGTGCCCTTGGCCAGGACCCAGACGTGTGGAAACTGCA  
CCTTCAGAGTCTGCTTTGAGCAGTGCTGCCCCTGGACCTTCATGGTGAAGCTGATAAACC  
AGAACTGCGACTCAGCCCGGACCTCGGATGACAGGCTTTGTGCGCAGTGTCAGCTTAATGGA  
ACATCAGGGGAACGATGACTCCTGGATTCTCCTTCCTGGGTGGGCCTGGAGAAAGAGGCT  
GGTGTTACCTGAGATCTGGGATGCTGAGTGGCTGTTTGGGGGCCAGAGAAACACACACTC  
AACTGCCCACTTCATTCTGTGACCTGTCTGAGGCCACCCTGCAGCTGCCCTGAGGAGGC  
CCACAGGTCCCCTTCTAGAATTCTGGACAGCATGAGATGCGTGTGCTGATGGGGGCCAG  
GGACTCTGAACCCCTCCTGATGACCCCTATGGCCAACATCAACCCGGCACCCCCCAAGGC  
TGGCTGGGGAACCCCTCACCCCTTCTGTGAGATTTTCCATCATCTCAAGTTCTTTCTATC  
CAGGAGCAAAGCACAGGATCATAATAAATTTATGTACTTTATAAATGAAAA

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## FIGURE 194

MAPRGCIVAVFAIFCISRLLC SHGAPVAPMTPYLMLCQPHKRCGDKFYDPLQHCCYDDAV  
VPLARTQTCGNCTFRVCFEQCCPWTFMVKLINQNCD SARTSDDRLCRSVS

**Signal peptide:**  
amino acids 1-24

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**FIGURE 195**

CATTTCCAACAAGAGCACTGGCCAAGTCAGCTTCTTCTGAGAGAGTCTCTAGAAGACATG  
ATGCTACACTCAGCTTTGGGTCTCTGCCTCTTACTCGTCACAGTTTCTTCCAACCTTGCC  
ATTGCAATAAAAAAGGAAAAGAGGCCTCCTCAGACACTCTCAAGAGGATGGGGAGATGAC  
ATCACTTGGGTACAACTTATGAAGAAGGTCTCTTTTATGCTCAAAAAAGTAAGAAGCCA  
TTAATGGTTATTCATCACCTGGAGGATTGTCAATACTCTCAAGCACTAAAGAAAGTATTT  
GCCCAAATGAAGAAATACAAGAAATGGCTCAGAATAAGTTCATCATGCTAAACCTTATG  
CATGAAACCACTGATAAGAATTTATCACCTGATGGGCAATATGTGCCTAGAATCATGTTT  
GTAGACCCTTCTTTAACAGTTAGAGCTGACATAGCTGGAAGATACTCTAACAGATTGTAC  
ACATATGAGCCTCGGGATTTACCCCTATTGATAGAAAACATGAAGAAAGCATTAAAGACTT  
ATTCAGTCAGAGCTATAAGAGATGATGGAAAAAAGCCTTCACTTCAAAGAAGTCAAATTT  
CATGAAGAAAACCTCTGGCACATTGACAAATACTAAATGTGCAAGTATATAGATTTTGTGTA  
ATATTACTATTTAGTTTTTTTTAATGTGTTTGCAATAGTCTTATTAAAATAAATGTTTTTT  
AAATCTGA

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**FIGURE 196**

MMLHSALGLCLLLVTVSSNLAIKKEKRPPQTL SRGWGDDITWVQTYEEGLFYAQKSKK  
PLMVIHHLEDCQYSQALKKVFAQNEEIQEMAQNKFIMLNLMHETTDKNLSPDGQYVPRIM  
FVDPSLTVRADIAGRYSNRLYTYEPRDLPLLIENMKKALRLIQSEL

**Important features:**

**Signal peptide:**

amino acids 1-23

**N-myristoylation site:**

amino acids 51-57

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**FIGURE 197**

GGGGGCGGGTGCCTGGAGCACGGCGCTGGGGCCGCCCCGAGCGCTCACTCGCTCGCACTC  
AGTCGCGGGAGGCTTCCCCGCGCCGCGCGTCCCCGCCGCTCCCCGGCACCAGAAGTTC  
CTCTGCGCGTCCGACGGCGACATGGGCGTCCCCACGGCCCTGGAGGCCGGCAGCTGGCGC  
TGGGGATCCCTGCTCTTCGCTCTCTTCCTGGCTGCGTCCCTAGGTCCGGTGGCAGCCTTC  
AAGGTCGCCACGCCGTATTCCCTGTATGTCTGTCCCGAGGGGCAGAACGTCACCCCTACC  
TGCAGGCTCTTGGGCCCTGTGGACAAAGGGCACGATGTGACCTTCTACAAGACGTGGTAC  
CGCAGCTCGAGGGGCGAGGTGCAGACCTGCTCAGAGCGCCGGCCCATCCGCAACCTCACG  
TTCCAGGACCTTCACCTGCACCATGGAGGCCACCAGGCTGCCAACACCAGCCACGACCTG  
GCTCAGCGCCACGGGCTGGAGTCGGCCTCCGACCACCATGGCAACTTCTCCATCACCATG  
CGCAACCTGACCCTGCTGGATAGCGGCCTCTACTGCTGCCTGGTGGTGGAGATCAGGCAC  
CACCCTCGGAGCACAGGGTCCATGGTGCCATGGAGCTGCAGGTGCAGACAGGCAAAGAT  
GCACCATCCAACCTGTGTGGTGTACCCATCCTCCTCCAGGATAGTGAAAACATCACGGCT  
GCAGCCCTGGCTACGGGTGCCTGCATCGTAGGAATCCTCTGCCCTCCCCCTCATCCTGCTC  
CTGGTCTACAAGCAAAGGCAGGCAGCCTCCAACCGCCGTGCCAGGAGCTGGTGC GGATG  
GACAGCAACATTCAAGGGATTGAAAACCCCGGCTTTGAAGCCTCACCACCTGCCAGGGG  
ATACCCGAGGCCAAAGTCAGGCACCCCTGTCTTATGTGGCCAGCGGCAGCCTTCTGAG  
TCTGGGCGGCATCTGCTTTCGGAGCCCAGCACCCCTGTCTCCTCCAGGCCCGGAGAC  
GTCTTCTTCCCATCCCTGGACCCTGTCCCTGACTCTCCAAACTTTGAGGTCATCTAGCCC  
AGCTGGGGGACAGTGGGCTGTTGTGGCTGGGTCTGGGGCAGGTGCATTTGAGCCAGGGCT  
GGCTCTGTGAGTGGCCTCCTTGGCCTCGGCCCTGGTTCCTCCTCCTGCTCTGGGCTCA  
GATACTGTGACATCCCAGAAGCCCAGCCCCCTCAACCCCTCTGGATGCTACATGGGGATGC  
TGGACGGCTCAGCCCCCTGTTCCAAGGATTTTGGGGTGCTGAGATTCTCCCCTAGAGACCT  
GAAATTCACCAGCTACAGATGCCAAATGACTTACATCTTAAGAAGTCTCAGAACGTCCAG  
CCCTTCAGCAGCTCTCGTTCTGAGACATGAGCCTTGGGATGTGGCAGCATCAGTGGGACA  
AGATGGACACTGGGCCACCCTCCCAGGCACCAGACACAGGGCACGGTGGAGAGACTTCTC  
CCCCGTGGCCGCCTTGGCTCCCCCGTTTTGCCCCAGGCTGCTCTTCTGTCAGACTTCCTC  
TTTGTACCACAGTGGCTCTGGGGCCAGGCCTGCCCTGCCCACTGGCCATCGCCACCTTCCC  
CAGCTGCCTCCTACCAGCAGTTTCTCTGAAGATCTGTCAACAGGTAAAGTCAATCTGGGG  
CTTCCACTGCCTGCATTCCAGTCCCCAGAGCTTGGTGGTCCCGAAACGGGAAGTACATAT  
TGGGGCATGGTGGCCTCCGTGAGCAAATGGTGTCTTGGGCAATCTGAGGCCAGGACAGAT  
GTTGCCCCACCCACTGGAGATGGTGTCTGAGGGAGGTGGGTGGGGCCTTCTGGGAAGGTGA  
GTGGAGAGGGGCACCTGCCCCCGCCCTCCCCATCCCCTACTCCCACTGCTCAGCGCGGG  
CCATTGCAAGGGTGCCACACAATGTCTTGTCCACCCTGGGACACTTCTGAGTATGAAGCG  
GGATGCTATTAAAACTACATGGGGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AGA

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**FIGURE 198**

MGVPTALEAGSWRWGSLFLFALFLAASLGPVAAFKVATPYSLYVCPEGQNVTLTCRLLGPV  
DKGHDVTFYKWTYRSSRGEVQTCSERRPIRNLTFQDLHLHHGGHQAANTSHDLAQRHGLE  
SASDHGNGFSITMRNLTLDDSGLYCCLVVEIRHHHSEHRVHGAMELQVQTGKDAPSNVCV  
YPSSSQDSENITAAALATGACIVGILCLPLILLLVYKQRQAASNRRAQELVRMDSNIQGI  
ENPGFEASPPAQGIPEAKVRHPLSYVAQRQPSESGRHLLSEPSTPLSPPGPGDVFFPSLD  
PVPDSPNFEVI

**Signal peptide:**  
amino acids 1-28

**Transmembrane domain:**  
amino acids 190-216



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**FIGURE 199**

CTAGCCTGCGCCAAGGGGTAGTGAGACCGCGCGGCAACAGCTTGCGGGCTGCGGGGAGCTC  
CCGTGGGCGCTCCGCTGGCTGTGCAGGCGGCCATGGATTCCCTTGCGGAAAATGCTGATCT  
CAGTCGCAATGCTGGGCGCAGGGGCTGGCGTGGGCTACGCGCTCCTCGTTATCGTGACCC  
CGGGAGAGCGGCGGAAGCAGGAAATGCTAAAGGAGATGCCACTGCAGGACCCAAGGAGCA  
GGGAGGAGGCGGCCAGGACCCAGCAGCTATTGCTGGCCACTCTGCAGGAGGCAGCGACCA  
CGCAGGAGAACGTGGCCTGGAGGAAGAACTGGATGGTTGGCGGCGAAGGCGGCGCCAGCG  
GGAGGTCAACCGTGAGACCGGACTTGCCCTCCGTGGGCGCCGGACCTTGGCTTGGGCGCAGG  
AATCCGAGGCAGCCTTTCTCCTTCGTGGGCCCAGCGGAGAGTCCGGACCGAGATAACCATG  
CCAGGACTCTCCGGGGTCTGTGAGCTGCCGTCCGGTGAGCACGTTTCCCCCAAACCTG  
GACTGACTGCTTTAAGGTCCGCAAGGCGGGCCAGGGCCGAGACGCGAGTCGGATGTGGTG  
AACTGAAAGAACCAATAAAATCATGTTCTCCAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 200

MDSLRLKMLISVAMLGAGAGVGYALLVIVTPGERRKQEMLKEMPLQDPRSREEAARTQQLL  
LATLQEAATTQENVAWRKNWMVGEGGASGRSP

**Signal peptide:**  
amino acids 1-18

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**FIGURE 201**

GACAGCTGTGTCTCGATGGAGTAGACTCTCAGAACAGCGCAGTTTGGCCCTCCGCTCACGC  
AGAGCCTCTCCGTGGCTTCCGCACCTTGAGCATTAGGCCAGTTCTCCTCTTCTCTCTAAT  
CCATCCGTCACCTCTCCTGTCATCCGTTTCCATGCCGTGAGGTCCATTACAGAACACAT  
CCATGGCTCTCATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAGTGGC  
AGGTGTTTGGGCCAGACAAGCCTGTCCAGGCCCTTGGTGGGGGAGGACGCAGCATTCTCCT  
GTTTCCTGTCTCCTAAGACCAATGCAGAGGCCATGGAAGTGCAGTTCTTTCAGGGGCCAGT  
TCTCTAGCGTGGTCCACCTCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATGCCAC  
AGTATCAAGGCAGGACAAAACCTGGTGAAGGATTCTATTGCGGAGGGGCGCATCTCTCTGA  
GGCTGGAAAACATTACTGTGTTGGATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGT  
CTTACTACCAGAAGGCCATCTGGGAGCTACAGGTGTCAGCACTGGGCTCAGTTCTCTCTCA  
TTTCCATCACGGGATATGTTGATAGAGACATCCAGCTACTCTGTCAGTCTTCGGGCTGGT  
TCCCCCGGCCCCACAGCGAAGTGGAAGGTCCACAAGGACAGGATTTGTCCACAGACTCCA  
GGACAAACAGAGACATGCATGGCCTGTTTGTATGTGGAGATCTCTCTGACCGTCCAAGAGA  
ACGCCGGGAGCATATCCTGTTCCATGCGGCATGCTCATCTGAGCCGAGAGGTGGAATCCA  
GGGTACAGATAGGAGATACCTTTTTTCGAGCCTATATCGTGGCACCTGGCTACCAAAGTAC  
TGGGAATACTCTGCTGTGGCCTATTTTTTGGCATTGTTGGACTGAAGATTTTCTTCTCCA  
AATTCCAGTGGAATAATCCAGGCGGAACTGGACTGGAGAAGAAAGCACGGACAGGCAGAAT  
TGAGAGACGCCCGGAAACACGCAGTGGAGGTGACTCTGGATCCAGAGACGGCTCACCCGA  
AGCTCTGCGTTTTCTGATCTGAAAACCTGTAACCCATAGAAAAGCTCCCCAGGAGGTGCCTC  
ACTCTGAGAAGAGATTTTACAAGGAAGAGTGTGGTGGCTTCTCAGAGTTTCCAAGCAGGGA  
AACATTACTGGGAGGTGGACGGAGGACACAATAAAAGGTGGCGCGTGGGAGTGTGCCGGG  
ATGATGTGGACAGGAGGAAGGAGTACGTGACTTTGTCTCCCGATCATGGGTACTGGGTCC  
TCAGACTGAATGGAGAACATTTGTATTTTACATTAAATCCCCGTTTTATCAGCGTCTTCC  
CCAGGACCCCACCTACAAAAATAGGGGTCTTCTTGACTATGAGTGTGGGACCATCTCCT  
TCTTCAACATAAATGACCAGTCCCTTATTTATACCCTGACATGTCGTTTTGAAGGCTTAT  
TGAGGCCCTACATTGAGTATCCGTCTTATAATGAGCAAAATGGAACCTCCATAGTCATCT  
GCCCAGTCACCCAGGAATCAGAGAAAGAGGCCTCTTGCAAAAGGGCCTCTGCAATCCCAG  
AGACAAGCAACAGTGAGTCTCCTCACAGGCAACCACGCCCTTCTCCCCAGGGGTGAAA  
TGATAGGATGAATCACATCCCACATTCTTCTTTAGGGATATTAAGGTCTCTCTCCAGATC  
CAAAGTCCCGCAGCAGCCGGCCAAGGTGGCTTCCAGATGAAGGGGGACTGGCCTGTCCAC  
ATGGGAGTCAGGTGTCATGGCTGCCCTGAGCTGGGAGGGAAGAAGGCTGACATTACATTT  
AGTTTGCTCTCACTCCATCTGGCTAAGTGATCTTGAAATACCACCTCTCAGGTGAAGAAC  
CGTCAGGAATTCCCATCTCACAGGCTGTGGTGTAGATTAAGTAGACAAGGAATGTGAATA  
ATGCTTAGATCTTATTGATGACAGAGTGTATCCTAATGGTTTGTTCATTATATTACACTT  
TCAGTAAAAAAA

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**FIGURE 202**

MALMLSLVLSLLKLGSGQWQVFGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFFRGQF  
SSVVHLYRDGKDQPFMQMPQYQGRTKLVKDSIAEGRISLRLENITVLDAGLYGCRISQS  
YYQKAIWELQVSALGSVPLISITGYVDRDIQLLCQSSGWFPRPTAKWKGPQGQDLSTDSR  
TNRDMHGLFDVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDTFFEPISWHLATKVL  
GILCCGLFFGIVGLKIFFSKFQWKIQAELDWRRKHGQAEIRDARKHAVEVTLDPETAHPK  
LCVSDLKTVTHRKAPEVPHSEKRFTRKSVVASQSFGAGKHYWEVDGGHNKRWRVGVCRD  
DVDRRKEYVTLSPDHGYWVLRNLNGEHLYFTLNPRFISVFPRTPTKIGVFLDYECGTISF  
FNINDQSLIYTLTCRFEGLLRPYIEYPSYNEQNGTPIVICPVTQESEKEASWQRASAIPE  
TSNSESSSQATTFFLPRGEM

**Signal peptide:**  
amino acids 1-17

**Transmembrane domain:**  
amino acids 239-255

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**FIGURE 203**

TGCGGCGCAGTG TAGACCTGGGAGGATGGGCGGCCTGCTGCTGGCTGCTTTTCTGGCTTT  
GGTCTCGGTGCCCAGGGCCCAGGCCGTGTGGTTGGGAAGACTGGACCCTGAGCAGCTTCT  
TGGGCCCTGGTACGTGCTTGC GGTGGCCTCCCGGGAAAAGGGCTTTGCCATGGAGAAGGA  
CATGAAGAACGTCGTGGGGGTGGTGGTGACCCTCACTCCAGAAAACAACCTGCGGACGCT  
GTCCTCTCAGCACGGGCTGGGAGGGTGTGACCAGAGTGTCATGGACCTGATAAAGCGAAA  
CTCCGGATGGGTGTTTGAGAATCCCTCAATAGGCGTGCTGGAGCTCTGGGTGCTGGCCAC  
CAACTTCAGAGACTATGCCATCATCTTCACTCAGCTGGAGTTCGGGGACGAGCCCTTCAA  
CACCGTGGAGCTGTACAGTCTGACGGAGACAGCCAGCCAGGAGGCCATGGGGCTCTTCAC  
CAAGTGGAGCAGGAGCCTGGGCTTCCTGTACAGTAGCAGGCCCAGCTGCAGAAGGACCT  
CACCTGTGCTCACAAGATCCTTCTGTGAGTGCTGCGTCCCCAGTAGGGATGGCGCCCACA  
GGGTCTGTGACCTCGGCCAGTGTCACCCACCTCGCTCAGCGGCTCCCGGGGCCAGCA  
CCAGCTCAGAATAAAGCGATTCCACAGCA

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**FIGURE 204**

MGGLLLAAFLALVSVPRQA VWLGR LDPEQL LGPWYVLAVASREKGFAMEKDMKNVVG VV  
VTLTPENNLRTLSSQHGLGGCDQSVMDLIKRN SGWVFENPSIGVLELWVLATNFRDYAI I  
FTQLEFGDEPFNTVELYSLTETASQEAMGLFTKWSRSLGFLSQ

**Signal peptide:**  
amino acids 1-20

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**FIGURE 205**

GACGCCCAGTGACCTGCCGAGGTCGGCAGCACAGAGCTCTGGAGATGAAGACCCTGTTCC  
TGGGTGTCACGCTCGGCCTGGCCGCTGCCCTGTCCTTCACCCTGGAGGAGGAGGATATCA  
CAGGGACCTGGTACGTGAAGGCCATGGTGGTCGATAAGGACTTTCCGGAGGACAGGAGGC  
CCAGGAAGGTGTCCCCAGTGAAGGTGACAGCCCTGGGCGGTGGGAAGTTGGAAGCCACGT  
TCACCTTCATGAGGGAGGATCGGTGCATCCAGAAGAAAATCCTGATGCGGAAGACGGAGG  
AGCCTGGCAAATACAGCGCCTATGGGGGCAGGAAGCTCATGTACCTGCAGGAGCTGCCCCA  
GGAGGGACCACTACATCTTTTACTGCAAAGACCAGCACCATGGGGGCCTGCTCCACATGG  
GAAAGCTTGTGGGTAGGAATTCTGATACCAACCGGGAGGCCCTGGAAGAATTTAAGAAAT  
TGGTGCAGCGCAAGGGACTCTCGGAGGAGGACATTTTCACGCCCCTGCAGACGGGAAGCT  
GCGTTCCCGAACACTAGGCAGCCCCCGGGTCTGCACCTCCAGAGCCCACCCTACCACCAG  
ACACAGAGCCCGGACCACCTGGACCTACCCTCCAGCCATGACCCTTCCCTGCTCCCACCC  
ACCTGACTCCAAATAAAGTCCTTTTCCCCCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAA

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**FIGURE 206**

MKTLFLGVTLGLAAALSFTLEEEEDITGTWYVKAMVVDKDFPEDRRPRKVSPVKVTALGGG  
KLEATFTFMREDRCIQKKILMRKTEEPGKYSAYGGRKLMYLQELPRRDHYIFYCKDQHHG  
GLLHMGKLVGRNSDTNREALEEFKKLVQRKGLSEEDIFTPLQTGSCVPEH

**Important features:**

**Signal peptide:**

amino acids 1-17



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**FIGURE 207**

GTTCCGCAGATGCAGAGGTTGAGGTGGCTGCGGGACTGGAAGTCATCGGGCAGAGGTCTC  
ACAGCAGCCAAGGAACCTGGGGCCCGCTCCTCCCCCTCCAGGCCATGAGGATTCTGCAG  
TTAATCCTGCTTGCTCTGGCAACAGGGCTTGTAGGGGGAGAGACCAGGATCATCAAGGGG  
TTCGAGTGCAAGCCTCACTCCCAGCCCTGGCAGGCAGCCCTGTTGAGAAGACGCGGCTA  
CTCTGTGGGGCGACGCTCATCGCCCCAGATGGCTCCTGACAGCAGCCCACTGCCTCAAG  
CCCCGCTACATAGTTACCTGGGGCAGCACAACCTCCAGAAGGAGGAGGGCTGTGAGCAG  
ACCCGGACAGCCACTGAGTCCTTCCCCACCCCGGCTTCAACAACAGCCTCCCCAACAAA  
GACCACCGCAATGACATCATGCTGGTGAAGATGGCATCGCCAGTCTCCATCACCTGGGCT  
GTGCGACCCCTCACCTCTCCTCACGCTGTGTCACTGCTGGCACCAGCTGCCTCATTTCC  
GGCTGGGGCAGCACGTCCAGCCCCAGTTACGCCTGCCTCACACCTTGCGATGCGCCAAC  
ATCACCATCATTGAGCACCAGAAGTGTGAGAACGCCTACCCCGGCAACATCACAGACACC  
ATGGTGTGTGCCAGCGTGCAGGAAGGGGGCAAGGACTCCTGCCAGGGTGACTCCGGGGGC  
CCTCTGGTCTGTAACCAGTCTCTTCAAGGCATTATCTCCTGGGGCCAGGATCCGTGTGCG  
ATCACCCGAAAGCCTGGTGTCTACACGAAAGTCTGCAAATATGTGGACTGGATCCAGGAG  
ACGATGAAGAACAATTAGACTGGACCCACCCACCACAGCCCATCACCTCCATTTCCACT  
TGGTGTTTGGTTCCTGTTCACTCTGTTAATAAGAAACCCTAAGCCAAGACCCTCTACGAA  
CATTCCTTTGGGCCTCCTGGACTACAGGAGATGCTGTCACTTAATAATCAACCTGGGGTTC  
GAAATCAGTGAGACCTGGATTCAAATTCTGCCTTGAAATATTGTGACTCTGGGAATGACA  
ACACCTGGTTTGTCTCTGTTGTATCCCAGCCCCAAAGACAGCTCCTGGCCATATATCA  
AGGTTTCAATAAATATTTGCTAAATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAA

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**FIGURE 208**

MRILQLILLALATGLVGGETRIIKGFECKPHSQPWQAALFEKTRLLCGATLIAPRWLLTA  
AHCLKPRYIVHLGQHNLOKEEGCEQTRTATESFPHPGFNNSLPNKDHRNDIMLVKMASPV  
SITWAVRPLTLSSRCVTAGTSCLISGWGSTSSPQLRLPHTLRCANITITIEHQKCENAYPG  
NITDTMVCASVQEGGKDSCQGDSSGGLVLCNQSLOGIISWGQDPCAITRKPGVYTKVCKYV  
DWIQETMKNN

**Important features:****Signal peptide:**

amino acids 1-18

**Serine proteases, trypsin family, histidine active site:**

amino acids 58-63

**N-glycosylation sites:**

amino acids 99-102, 165-168, 181-184, 210-213

**Glycosaminoglycan attachment site:**

amino acids 145-148

**Kringle domain proteins:**

amino acids 197-209, 47-64

**Serine proteases, trypsin family, histidine protein:**

amino acids 199-209, 47-63, 220-243

**Apple domain proteins:**

amino acids 222-249, 189-222

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**FIGURE 209**

GCGGCCACACGCAGCTAGCCGGAGCCCGGACCAGGCGCCTGTGCCTCCTCCTCGTCCCTC  
GCCGCGTCCGCGAAGCCTGGAGCCGGCGGGAGCCCCGCGCTCGCCATGTCGGGCGAGCTC  
AGCAACAGGTTCCAAGGAGGGAAGGCGTTCGGCTTGCTCAAAGCCCGGCAGGAGAGGAGG  
CTGGCCGAGATCAACCGGGAGTTTCTGTGTGACCAGAAGTACAGTGATGAAGAGAACCTT  
CCAGAAAAGCTCACAGCCTTCAAAGAGAAGTACATGGAGTTTGACCTGAACAATGAAGGC  
GAGATTGACCTGATGTCTTTAAAGAGGATGATGGAGAAGCTTGGTGTCCCCAAGACCCAC  
CTGGAGATGAAGAAGATGATCTCAGAGGTGACAGGAGGGGTGAGTGACACTATATCCTAC  
CGAGACTTTGTGAACATGATGCTGGGGAAACGGTCGGCTGTCTCAAGTTAGTCATGATG  
TTTGAAGGAAAAGCCAACGAGAGCAGCCCCAAGCCAGTTGGCCCCCTCCAGAGAGAGAC  
ATTGCTAGCCTGCCCTGAGGACCCCGCCTGGACTCCCCAGCCTTCCACCCCATACCTCC  
CTCCCGATCTTGCTGCCCTTCTTGACACACTGTGATCTCTCTCTCTCATTGTGTTGGT  
CATTGAGGGTTTGTGTTGTGTTTTTCATCAATGTCTTTGTAAAGCACAAATTATCTGCCTTA  
AAGGGGCTCTGGGTCGGGGAATCCTGAGCCTTGGGTCCCCTCCCTCTCTTCTTCCCTCCT  
TCCCCGCTCCCTGTGCAGAAGGGCTGATATCAAACCAAAAAGTAGAGGGGGCAGGGCCAG  
GGCAGGGAGGCTTCCAGCCTGTGTTCCCCCTCACTTGGAGGAACCAGCACTCTCCATCCTT  
TCAGAAAAGTCTCCAAGCCAAGTTCAGGCTCACTGACCTGGCTCTGACGAGGACCCAGGC  
CACTCTGAGAAGACCTTGGAGTAGGGACAAGGCTGCAGGGCCTCTTTTCGGGTTTCCTTGG  
ACAGTGCCATGGTTCCAGTGCTCTGGTGTCAACCAGGACACAGCCACTCGGGGCCCCGCT  
GCCCCAGCTGATCCCCACTCATTCCACACCTCTTCTCATCCTCAGTGATGTGAAGGTGGG  
AAGGAAAGGAGCTTGGCATTGGGAGCCCTTCAAGAAGGTACCAGAAGGAACCCTCCAGTC  
CTGCTCTCTGGCCACACCTGTGCAGGCAGCTGAGAGGCAGCGTGACGCCCTACTGTCCCT  
TACTGGGGCAGCAGAGGGCTTCGGAGGCAGAAGTGAGGCCTGGGGTTTGGGGGAAAGGT  
CAGCTCAGTGCTGTTCCACCTTTTAGGGAGGATACTGAGGGGACCAGGATGGGAGAATGA  
GGAGTAAAATGCTCACGGCAAAGTCAGCAGCACTGGTAAGCCAAGACTGAGAAATACAAG  
GTTGCTTGTCTGACCCCAATCTGCTTGAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 210

MSGELSNRFQGGKAFGLLKARQERRLAEGINREFLCDQKYSDEENLPEKLTAFKEKYMEFD  
LNNEGEIDLMSLKRMMEKLGVPKTHLEMKKMISEVTGGVSDTISYRDFVNMMLGKRSAVL  
KLVMMFEGKANESSPKPVGPPPERDIASLP

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**FIGURE 211**

CTGGGATCAGCCACTGCAGCTCCCTGAGCACTCTCTACAGAGACGCGGACCCCAGACATG  
AGGAGGCTCCTCCTGGTCACCAGCCTGGTGGTTGTGCTGCTGTGGGAGGCAGGTGCAGTC  
CCAGCACCCAAGGTCCCTATCAAGATGCAAGTCAAACACTGGCCCTCAGAGCAGGACCCA  
GAGAAGGCCTGGGGCGCCCGTGTGGTGGAGCCTCCGGAGAAGGACGACCAGCTGGTGGTG  
CTGTTCCCTGTCCAGAAGCCGAAACTCTTGACCACCGAGGAGAAGCCACGAGGTCAGGGC  
AGGGGCCCCATCCTTCCAGGCACCAAGGCCTGGATGGAGACCGAGGACACCCTGGGCCGT  
GTCCTGAGTCCCGAGCCCGACCATGACAGCCTGTACCACCCTCCGCCTGAGGAGGACCAG  
GGCGAGGAGAGGCCCCGGTTGTGGGTGATGCCAAATCACCAGGTGCTCCTGGGACCGGAG  
GAAGACCAAGACCACATCTACCACCCCCAGTAGGGGCTCCAGGGGCCATCACTGCCCCCGC  
CCTGTCCCAAGGCCCAGGCTGTTGGGACTGGGACCCTCCCTACCCTGCCCCAGCTAGACA  
AATAAACCCCAGCAGGCAAAAAAAAAAAAAAAAAAAAAA

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## FIGURE 212

MRRLLLVTSLVVLLWEAGAVPAPKVPIKMQVKHWPSEQDPEKAWGARVVEPPEKDDQLV  
VLFPVQKPKLLTTEEKPRGQGRGPILPGTKAWMETEDTLGRVLSPEPDHDSLYHPPPEED  
QGEERPRLWVMPNHQVLLGPEEDQDHIYHPQ

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**FIGURE 213**

CAGGCAGAAGCGAACAAAGACCCAGCAAGAGAAGGCAGAGGCTAAGACCCATCCCGTATC  
TGCTCTCCTGAAATAATTCTGGAGTCATGCCTGAAATGCCAGAGGACATGGAGCAGGAGG  
AAGTTAACATCCCTAATAGGAGGGTTCTGGTTACTGGTGCCACTGGGCTTCTTGGCAGAG  
CTGTACACAAAGAATTTTCAGCAGAATAATTGGCATGCAGTTGGCTGTGGTTTCAGAAGAG  
CAAGACCAAAATTTGAACAGGTAACTCTGTTGGATTCTAATGCAGTTCATCACATCATTC  
ATGATTTTTCAGCCCCATGTTATAGTACATTGTGCAGCAGAGAGAAGACCAGATGTTGTAG  
AAAATCAGCCAGATGCTGCCTCTCAACTTAATGTGGATGCTTCTGGGAATTTAGCAAAGG  
AAGCAGCTGCTGTTGGAGCATTCTCATCTACATTAGCTCAGATTATGTATTTGATGGAA  
CAAATCCACCTTACAGAGAGGAAGACATACCAGCTCCCCTAAATTTGTATGGCAAACAA  
AATTAGATGGAGAAAAGGCTGTCTGGAGAACAATCTAGGAGCTGCTGTTTTGAGGATTC  
CTATTCTGTATGGGGAAGTTGAAAAGCTCGAAGAAAAGTGCTGTGACTGTTATGTTTGATA  
AAGTGCAGTTTCAGCAACAAGTCAGCAACATGGATCACTGGCAGCAGAGGTTCCCCACAC  
ATGTCAAAGATGTGGCCACTGTGTGCCGCGCAGCTAGCAGAGAAGAGAATGCTGGATCCAT  
CAATTAAGGGAACCTTTCACTGGTCTGGCAATGAACAGATGACTAAGTATGAAATGGCAT  
GTGCAATTGCAGATGCCTTCAACCTCCCAGCAGTCACCTAAGACCTATTACTGACAGCC  
CTGTCTTAGGAGCACACGTCGAGAAATGCTCAGCTTGACTGCTCCAAATTGGAGACCT  
TGGGCATTGGCCAACGAACACCATTTTGAATTTGGAATCAAAGAATCACTTTGGCCTTTCC  
TCATTGACAAGAGATGGAGACAAACGGTCTTTCATTAGTTTTATTTGTGTTGGGTTCTTTT  
TTTTTTTTAAATGAAAAGTATAGTATGTGGCACTTTTTAAAGAACAAGGAAATAGTTTTG  
TATGAGTACTTTAATTGTGACTCTTAGGATCTTTCAGGTAAATGATGCTCTTGCACTAGT  
GAAATTGTCTAAAGAACTAAAGGGCAGTCATGCCCTGTTTGCAGTAATTTTTCTTTTAA  
TCATTTTGTGTTGTCCTGGCTAACTTGGAGTTTGAGTATAGTAAATTATGATCCTTAAAT  
ATTTGAGAGTCAGGATGAAGCAGATCTGCTGTAGACTTTTCAGATGAAATTGTTTATTCT  
CGTAACCTCCATATTTTCAGGATTTTGAAGCTGTTGACCTTTTCATGTTGATTATTTTA  
AATTGTGTGAAATAGTATAAAAATCATTGGTGTTCATTATTTGCTTTGCCTGAGCTCAGA  
TCAAAATGTTTGAAGAAAGGAACCTTTATTTTGAAGTTACGTACAGTTTTTATGCTTGA  
GATATTTCAACATGTTATGTATATTGGAACCTCTACAGCTTGATGCCTCCTGCTTTTATA  
GCAGTTTATGGGGAGCACTTGAAAGAGCGTGTGTACATGTATTTTTTTCTAGGCAAACA  
TTGAATGCAAACGTGTATTTTTTTAATATAAATATAAAGTGTCTTTTCATCCCATGTT  
GCCGCTAAGTGATATTTTCATATGTGTGGTTATACTCATAATAATGGGCCTTGTAAGTCTT  
TTCACCATTCATGAATAATAAATATGTACTGCTGGCATGTAATGCTTAGTTTTCTTG  
TATTTACTTCTTTTTTTAAATGTAAGGACCAACTTCTAACTAATTGTTCTTTTGTGTC  
TTTAATTTTTTAAATTAACATTCTTCTGATGTAACATGTGATACATAAAAGAATATAG  
TTTAATATGTATTGAAATAAAACACAATAAAAT

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**FIGURE 214**

MPEMPEDMEQEEVNIPNRRVLVTGATGLLGRAVHKEFQQNNWHAVGCGFRRARPKFEQVN  
LLDSNAVHHIIHDFQPHVIVHCAAERRPDVVENQPDAAASQLNVDASGNLAKEAAAVGAFL  
IYISSDYVFDGTNPPYREEDIAPAPLNLYGKTKLDGEKAVLENNLGA AVLRIPILYGEVEK  
LEESAVTVMFDKVQFSNKSANMDHWQQRFP THVKDVATVCRQLAEKRMLDPSIKGTFHWS  
GNEQMTKYEMACAIADAFNLPSSHLRPITDSPVLGAQRPRNAQLDCSKLET LGIGQRTPF  
RIGIKESLWPFLIDKRWRQTVFH

**Signal peptide:**  
amino acids 1-30

**Transmembrane domain:**  
amino acids 105-127

**N-glycosylation site:**  
amino acids 197-201

**N-myristoylation site:**  
amino acids 303-309

**Short-chain dehydrogenases/reductases family proteins:**  
amino acids 18-30



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**FIGURE 215**

GTGAATGTGAGGGTTTGATGACTTTCAGATGTCTAGGAACCAGAGTGGGTGCAGGGGCCC  
CAGGCAGGGCTGATTCTTGGGCGGAGGAGAGTAGGGTAAAGGGTTCTGCATGAGCTCCTT  
AAAGGACAAAGGTAACAGAGCCAGCGAGAGAGCTCGAGGGGAGACTTTGACTTCAAGCCA  
CAGAATTGGTGAAGTGTGCGCGCCGCCGCCGCTCGCTCCTGCAGCGCTGTGACCTA  
GCCGCTAGCATCTTCCCGAGCACCGGGATCCCGGGGTAGGAGGCGACGCGGGCGAGCACC  
AGCGCCAGCCGGCTGCGGCTGCCACACGGCTCACCATGGGCTCCGGGCGCCGGGCGCTG  
TCCGCGGTGCCGGCCGTGCTGCTGGTCCTCACGCTGCCGGGGCTGCCCGTCTGGGCACAG  
AACGACACGGAGCCCATCGTGTGGAGGGCAAGTGTCTGGTGGTGTGCGACTCGAACCCG  
GCCACGGACTCCAAGGGCTCCTCTTCCCTCCCGCTGGGGATATCGGTCCGGGCGGCCAAC  
TCCAAGGTCGCCCTTCTCGGCGGTGCGGAGCACCAACCACGAGCCATCCGAGATGAGCAAC  
AAGACGCGCATCATTTACTTCGATCAGATCCTGGTGAATGTGGGTAATTTTTTTCATTG  
GAGTCTGTCTTTGTAGCACCAAGAAAAGGAATTTACAGTTTCAGTTTTTCACGTGATTAAA  
GTCTACCAGAGCCAACTATCCAGGTAACTTGATGTTAAATGGAAAAACCAGTAATATCT  
GCCTTTGCGGGGGACAAAGATGTTACTCGTGAAGCTGCCACGAATGGTGTCTGCTCTAC  
CTAGATAAAGAGGATAAGGTTTACCTAAAACTGGAGAAAGGTAATTTGGTTGGAGGCTGG  
CAGTATTCCACGTTTTCTGGCTTTCTGGTGTTCCTCCCTATAGGATTCAATTTCTCCATGA  
TGTTTCATCCAGGTGAGGGATGACCCACTCCTGAGTTATTGGAAGATCATTTTTTTCATCAT  
TGGATTGATGTCTTTTATTGGTTTCTCATGGGTGGATATGGATTCTAAGGATTCTAGCCT  
GTCTGAACCAATACAAAATTTACAGATTATTTGTGTGTGTCTGTTTCAGTATATTTGGA  
TTGGGACTCTAAGCAGATAATACCTATGCTTAAATGTAACAGTCAAAGCTGTCTGCAAG  
ACTTATTCTGAATTTCAATTCCTGGGATTACTGAATTAGTTACAGATGTGGAATTTTATT  
TGTTTAGTTTTTAAAGACTGGCAACCAGGTCTAAGGATTAGAAAACCTAAAGTTCTGAC  
TTCAATCAACGGTTAGTGTGATACTGCCAAAGAACTGTATACTGTGTTAATATATTGATT  
ATATTTGTTTTTATTCCCTTTGGAATTAGTTTGTTTGGTTCTTGTAAAAACTTGGATTTT  
TTTTTTTCAGTAACTGGTATTATGTTTTCTCTTAAATAAGGTAATGAATGGCTTGCCAC  
AAATTTACCTTGACTACGATATCATCGACATGACTTCTCTCAAAAAAAGAATGCTTCA  
TAGTTGTATTTTAATTGTATATGTGAAAGAGTCATATTTTCCAAGTTATATTTTCTAAGA  
AGAAGAATAGATCATAAATCTGACAAGGAAAAAGTTGCTTACCCAAAATCTAAGTGCTCA  
ATCCCTGAGCCTCAGCAAAACAGCTCCCCTCCGAGGGAAATCTTATACTTTATTGCTCAA  
CTTTAATTAAATGATTGATAATAACCACTTTATTAAAAACCTAAGGTTTTTTTTTTTTC  
CGTAGACATGACCACTTTATTAAGTGGTGGGATGCTGTTGTTTCTAATTATACCTAT  
TTTTCAAGGCTTCTGTTGTATTTGAAGTATCATCTGGTTTTGCCTTAACTCTTTAAATTG  
TATATATTTATCTGTTTAGCTAATATTAAATTCAAATATCCCATATCTAAATTTAGTGCA  
ATATCTTGTCTTTTGTATAGGTCATATGAATTCATAAAATTATTTATGTCTGTTATAGAA  
TAAAGATTAATATATGTTAAAAAAA

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**FIGURE 216**

MGSGRRALSAVPAVLLVLTLPGLPVWAQNDTEPIVLEGKCLVVCDSNPATDSKGSSSSPL  
GISVRAANSKVAFAVRSTNHEPSEMSNKTRI IYFDQILVNVGNFFTLESVVFVAPRKG IY  
SFSFHVIK VYQSQT IQVNLMLNGKPVISAFAGDKDVTREAAATNGVLLYLDKEDKVYLKLE  
KGNLVGGWQYSTFSGFLVFPL

**Signal peptide:**  
amino acids 1-27

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**FIGURE 217**

CGGCAACCAGCCGCCGCCACCACCGCTGCCACTGCCGCCCTGCCGGGGCCATGTTCGCTC  
TGGGCTTGCCCTTCTTGGTGCTCTTGGTGGCCTCGGTTCGAGAGCCATCTGGGGGTTCCTGG  
GGCCCAAGAACGTCTCGCAGAAAGACGCCGAGTTTGAGCGCACCTACGTGGACGAGGTCA  
ACAGCGAGCTGGTCAACATCTACACCTTCAACCATACTGTGACCCGCAACAGGACAGAGG  
GCGTGCGTGTGTCTGTGAACGTCTGAACAAGCAGAAGGGGGCGCCGTTGCTGTTTGTGG  
TCCGCCAGAAGGAGGCTGTGGTGTCTTCCAGGTGCCCCTAATCCTGCGAGGGATGTTTC  
AGCGCAAGTACCTCTACCAAAAAGTGGAACGAACCCTGTGTGACCCCCCACCAAGAATG  
AGTCGGAGATTCACTTCTACGTGGATGTGTCCACCCTGTCACCAGTCAACACCACAT  
ACCAGCTCCGGGTCAGCCGCATGGACGATTTTGTGCTCAGGACTGGGGAGCAGTTCAGCT  
TCAATACCACAGCAGCACAGCCCCAGTACTTCAAGTATGAGTTCCTGAAGGCGTGGACT  
CGGTAATTGTCAAGGTGACCTCCAACAAGGCCTTCCCCTGCTCAGTCATCTCCATTCAGG  
ATGTGCTGTGTCTGTCTATGACCTGGACAACAACGTAGCCTTCATCGGCATGTACCAGA  
CGATGACCAAGAAGGCGGCCATCACCGTACAGCGCAAAGACTTCCCCAGCAACAGCTTTT  
ATGTGGTGGTGGTGGTGAAGACCGAAGACCAAGCCTGCGGGGGCTCCCTGCCTTTCTACC  
CCTTCGCAGAAGATGAACCGGTGATCAAGGGCACCGCCAGAAAACCTGTGAGTGCTGG  
TGTCTCAAGCAGTCACGTCTGAGGCATACGTGAGTGGGATGCTCTTTTGCCTGGGTATAT  
TTCTCTCCTTTTACCTGCTGACCGTCCTCCTGGCCTGCTGGGAGAAGTGGAGGCAGAAGA  
AGAAGACCCTGCTGGTGGCCATTGACCGAGCCTGCCAGAAAGCGGTACCCCTCGAGTCC  
TGGCTGATTCTTTTCCCTGGCAGTTCCCCTTATGAGGGTTACAACCTATGGCTCCTTTGAGA  
ATGTTTCTGGATCTACCGATGGTCTGGTTGACAGCGCTGGCACTGGGGACCTCTCTTACG  
GTTACCAGGGCCGCTCCTTTGAACCTGTAGGTACTCGCCCCGAGTGGACTCCATGAGCT  
CTGTGGAGGAGGATGACTACGACACATTGACCGACATCGATTCCGACAAGAATGTCATTC  
GCACCAAGCAATACCTCTATGTGGCTGACCTGGCACGGAAGGACAAGCGTGTTCTGCGGA  
AAAAGTACCAGATCTACTTCTGGAACATTGCCACCATTGCTGTCTTCTATGCCCTTCCTG  
TGGTGCAGCTGGTGATCACCTACCAGACGGTGGTGAATGTCACAGGGAATCAGGACATCT  
GCTACTACAACCTCCTCTGCGCCCACTGGGCAATCTCAGCGCCTTCAACAACATCC  
TCAGCAACCTGGGGTACATCCTGCTGGGGCTGCTTTTCCCTGCTCATCATCCTGCAACGGG  
AGATCAACCACAACCGGGCCCTGCTGCGCAATGACCTCTGTGCCCTGGAATGTGGGATCC  
CCAAACACTTTGGGCTTTTCTACGCCATGGGCACAGCCCTGATGATGGAGGGGCTGCTCA  
GTGCTTGCTATCATGTGTGCCCCAACTATAACCAATTTCCAGTTTGACACATCGTTCATGT  
ACATGATCGCCGACTCTGCATGCTGAAGCTCTACCAGAAGCGGCACCCGGACATCAACG  
CCAGCGCCTACAGTGCCCTACGCCTGCCTGGCCATTGTGATCTTCTTCTCTGTGCTGGGCG  
TGGTCTTTGGCAAAGGGAACACGGCGTTCTGGATCGTCTTCTCCATCATTCACATCATCG  
CCACCCTGCTCCTCAGCACGCAGCTCTATTACATGGGCCGGTGGAAACTGGACTCGGGGA  
TCTTCCGCCGCATCCTCCACGTGCTCTACACAGACTGCATCCGGCAGTGCAGCGGGCCGC  
TCTACGTGGACCGCATGGTGTGCTGGTTCATGGGCAACGTGATCAACTGGTCGCTGGCTG  
CCTATGGGCTTATCATGCGCCCCAATGATTTGCTTCTTACTTGTGGCCATTGGCATCT  
GCAACCTGCTCCTTTACTTCGCCTTCTACATCATCATGAAGCTCCGGAGTGGGGAGAGGA  
TCAAGCTCATCCCCCTGCTCTGCATCGTTTGACCTCCGTGGTCTGGGGCTTCGCGCTCT  
TCTTCTTCTTCCAGGGACTCAGCACCTGGCAGAAAACCCCTGCAGAGTCGAGGGAGCACA  
ACCGGGACTGCATCCTCCTCGACTTCTTTGACGACCACGACATCTGGCACTTCTCTCCT  
CCATCGCCATGTTTCGGGTCTTCTCCTGGTGTGCTGACACTGGATGACGACCTGGATACTG  
TGCAGCGGGACAAGATCTATGTCTTCTAGCAGGAGCTGGGCCCTTCGCTTCACCTCAAGG  
GGCCCTGAGCTCCTTTGTGTGTCATAGACCGGTCACTCTGTGCTGCTGTGGGGATGAGTCCC  
AGCACCGCTGCCAGCACTGGATGGCAGCAGGACAGCCAGGTCTAGCTTAGGCTTGGCCT  
GGGACAGCCATGGGGTGGCATGGAACCTTGCAGCTGCCCTCTGCCGAGGAGCAGGCCTGC  
TCCCCTGGAACCCCCAGATGTTGGCCAAATTGCTGCTTCTTCTCAGTGTTGGGGCCTTC

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CATGGGCCCCCTGTCCTTTGGCTCTCCATTTGTCCCTTTGCAAGAGGAAGGATGGAAGGGA  
CACCTCCCCATTTTCATGCCTTGCAATTTGCCCCGTCTCCTCCCCACAATGCCCCAGCCT  
GGGACCTAAGGCCTCTTTTCTCCCTCCATACTCCCACTCCAGGGCCTAGTCTGGGGCCTGA  
ATCTCTGTCCTGTATCAGGGCCCCAGTTCTCTTTGGGCTGTCCCTGGCTGCCATCACTGC  
CCATTCCAGTCAGCCAGGATGGATGGGGGTATGAGATTTTGGGGGTGGCCAGCTGGTGC  
CAGACTTTTGGTGCTAAGGCCTGCAAGGGGCCTGGGGCAGTGCGTATTCTCTTCCCTCTG  
ACCTGTGCTCAGGGCTGGCTCTTTAGCAATGCGCTCAGCCCAATTTGAGAACCGCCTTCT  
GATTCAAGAGGCTGAATTCAGAGGTCACCTCTTCATCCCATCAGCTCCCAGACTGATGCC  
AGCACCAGGACTGGAGGGAGAAGCGCCTCACCCCTTCCCTTCCTTCTTTCCAGGCCCTTA  
GTCTTGCCAAACCCCAGCTGGTGGCCTTTTCAGTGCCATTGACACTGCCCAAGAATGTCCA  
GGGGCAAAGGAGGGATGATACAGAGTTCAGCCCGTTCTGCCTCCACAGCTGTGGGCACCC  
CAGTGCCCTACCTTAGAAAGGGGCTTCAGGAAGGGATGTGCTGTTTCCCTCTACGTGCCCA  
GTCCTAGCCTCGCTCTAGGACCCAGGGCTGGCTTCTAAGTTTCCGTCCAGTCTTCAGGCA  
AGTTCTGTGTTAGTCATGCACACACATACCTATGAAACCTTGGAGTTTACAAAGAATTGC  
CCCAGCTCTGGGCACCCCTGGCCACCCTGGTCTTGGATCCCCTTCGTCCACCTGGTCCA  
CCCCAGATGCTGAGGATGGGGGAGCTCAGGCGGGGCCTCTGCTTTGGGGATGGGAATGTG  
TTTTTCTCCCAAACCTTGTTTTTATAGCTCTGCTTGAAGGGCTGGGAGATGAGGTGGGTCT  
GGATCTTTTCTCAGAGCGTCTCCATGCTATGGTTGCATTTCCGTTTTCTATGAATGAATT  
TGCAATCAATAAACAACCAGACTCAAAAAAAAAAAAAA

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**FIGURE 218**

MFALGLPFLVLLVASVESHLGVLGPKNVSQKDAEFERTYVDEVNSELVNIYTFNHTVTRN  
RTEGVRVSVNVLNKQKGAPLLFVVRQKEAVVSFQVPLILRGMFQRKYLYQKVERTLCQPP  
TKNESEIQFFYVDVSTLSPVNTTYQLRVSRMDDFVLRTEGEQFSFNTTAAQPQYFKYEFPE  
GVDSVIVKVTSNKAFPCSVISIQDVLCPVYDLNNAVFIGMYQTMTKKAITVQRKDFPS  
NSFYVVVVVKTEDQACGGS LPFYPPFAEDEPVDQGHRQKTL SVLV SQAVTSEAYVSGMLFC  
LGIFLSFYLLTVLLACWENWRQKKKTLLVAIDRACPESGHPRVLADSFPGSSPYEGYNYG  
SFENVSGSTDGLVDSAGTGDLSYGYQGRSFEPVGTRPRVDSMSSVEEDDYDTLTDIDSDK  
NVIRTKQYLYVADLARKDKRVLRRKKYQIYFVNIATIAVFYALPVVQLVITYQTVVNVNVTGN  
QDICYYNFLCAHPLGNLSAFNNILSNLGYILLGLLFLLIILQREINHNRALLRNDLCALC  
CGIPKHFGLFYAMGTALMMEGLLSACYHVC PNYTNFQFDTSFMYMIAGLCMLKLYQKRHP  
DINASAYSAYACLAIVIFFSVLGVVFGKGNTAFWIVFSIIHIIATLLLSTQLYYMGRWKL  
DSGIFRRILHVLYTDCIRQCSGPLYVDRMVLVVMGNVINWSLAAYGLIMRPNDFASYLLA  
IGICNLLLYFAFYIIMKLRSGERIKLIPLLCIVCTSVVWGFALFFFFQGLSTWQKTPAES  
REHNRDCILLDFDDHDIWHFLSSIAMFGSFLVLLTLDDDLDTVQRDKIYVF

**Important features of the protein:****Signal peptide:**

amino acids 1-18

**Transmembrane domains:**

amino acids 292-317, 451-470, 501-520, 607-627, 751-770

**Leucine zipper pattern:**

amino acids 497-518

**N-glycosylation sites:**amino acids 27-30, 54-57, 60-63, 123-126, 141-144, 165-168,  
364-367, 476-479, 496-499, 572-575, 603-606, 699-702

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**FIGURE 219**

[illegible]

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**FIGURE 220**

MRSTILLFCLLGSTRSLPQLKPALGLPPTKLAPDQGTLPNQQQSNQVFPSLSLIPLTQML  
TLGPDHLHLLNPAAGMTPGTQTHPLTLGGLNVQQQLHPHVLPIFVTQLGAQGILSSEELP  
QIFTSLIIHSLFPGGILPTSQAGANPDVQDGSLPAGGAGVNPATQGTPAGRLPTPSGTDD  
DFAVTTPAGIQRSTHAIEEATTESANGIQ

Signal peptide:  
amino acids 1-16





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**FIGURE 222**

MARMSFVIAACQLVLGLLMTSLTESSIONSECPQLCVCEIRPWFTPQSTYREATTVDCND  
LRLTRIPSNLSSDTQVLLQLSNNIAKTVDELQQLFNLTELDIFSQNNFTNIKEVGLANLTQ  
LTTLHLEENQITEMTDYCLQDLSNLQELYINHNQISTISAHAFAGLKNNLLRLHLNSNKLK  
VIDSRWFDSTPNLEILMIGENPVIGILDMNFKPLANLRSLVLAGMYLTDIPGNALVGLDS  
LESLSFYDNKLVKVPQLALQKVPNLKFLDLNKNPIHKIQEGDFKNMLRLKELGINNMGEL  
VSVDRYALDNLPELTKEATNNPKLSYIHLAFRSVPALSLMLNNNALNAIYQKTVESL  
PNLREISIHNSNPLRCDLVIHWINSNKTNIIRFMEPLSMFCAMPPEYKQGHQVKEVLIQDSSE  
QCLPMISHDSFPNRLNVDIGTTVFLDCRAMAEPEPEIYWVTPIGNKITVETLSDKYKLSS  
EGTLEISNIQIEDSGRYTCVAQNVQGADTRVATIKVNGTLLDGTQVLKIYVKQTESHSL  
VSWKVNSNVMTSNLKWSSATMKIDNPHITYTARVPVDVHEYNLTHLQPSDYEVCCLTVSN  
IHQQTQKSCVNVTTKNAFAVDISDQETSTALAAVMGSMFAVISLASIAVYFAKRFRKN  
YHHSLLKKYMQKTSSIPLNELYPPPLINLWEGDSEKDKDGSADTKPTQVDTSRSYMW

**Important features:****Signal peptide:**

Amino acids 1-25

**Transmembrane domain:**

Amino acids 508-530

**N-glycosylation sites:**Amino acids 69-73;96-100;106-110;117-121;385-389;517-521;  
582-586;611-615**Tyrosine kinase phosphorylation site:**

Amino acids 573-582

**N-myristoylation sites:**

Amino acids 16-22;224-230;464-470;637-643;698-704

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### FIGURE 223

[illegible]

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**FIGURE 224**

MASYLYGVLFVAVGLCAPIYCVSPANAPSAYPRPSSTKSTPASQVYSLNTDFAFRLYRRLV  
LETPSQNIFFSPVSVSTSLAMLSLGAHSVTKTQILQGLGFNLTHTPESAIHQGFQHLVHS  
LTVPSKDLTLKMGSALFVKKELQLQANFLGNVKRLYEAEVFSTDFSNPSIAQARINSHVK  
KKTQGKVVDIIQGLDLLTAMVLVNHIFFKAKWEKPFHLEYTRKNFPFLVGEQVTVQVPMM  
HQKEQFAFGVDTELNCFVLQMDYKGDVAFFVLPSKGKMRQLEQALSARTLIKWSHSLQK  
RWIEVFIPRFSISASYNLETILPKMGIQNAFDKNADFSGIKRDSLQVSKATHKAVLDVS  
EEGTEATAATTTKFIVRSKDGPSYFTVSFNRTFLMMITNKATDGILFLGKVENPTKS

**Signal peptide:**  
amino acids 1-20

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**FIGURE 225**

GGGAGAGAGGATAAATAGCAGCGTGGCTTCCCTGGCTCCTCTCTGCATCCTTCCCGACCT  
TCCCAGCAATATGCATCTTGACAGTCTGGTCGGCTCCTGCTCCCTCCTTCTGCTACTGGG  
GGCCCTGTCTGGATGGGCGGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAA  
CCGAGGGCTGAGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGG  
AATCACGCATGCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAG  
CCACACCGGCAAGGAGTTGGACAAAGGCGTCCAGGGGCTCAACCACGGCATGGACAAGGT  
TGCCCATGAGATCAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCA  
TGGGGTCAACAACGCTGCTGGACAGGCCGGGAAGGAAGCAGACAAAGCGGTCCAAGGGTT  
CCCACTGGGGTCCACCAGGCTGGGAAGGAAGCAGAGAACTTGGCCAAGGGGTCAACCA  
TGCTGCTGACCAGGCTGGAAAGGAAGTGGAGAAGCTTGGCCAAGGTGCCCACCATGCTGC  
TGGCCAGGCCGGGAAGGAGCTGCAGAATGCTCATAATGGGGTCAACCAAGCCAGCAAGGA  
GGCCAACCAGCTGCTGAATGGCAACCATCAAAGCGGATCTTCCAGCCATCAAGGAGGGGC  
CACAACCACGCCGTTAGCCTCTGGGGCCTCAGTCAACACGCCTTTCATCAACCTTCCCGC  
CCTGTGGAGGAGCGTCGCCAACATCATGCCCTAAACTGGCATCCGGCCTTGCTGGGAGAA  
TAATGTCGCCGTTGTCACATCAGCTGACATGACCTGGAGGGGTTGGGGGTGGGGGACAGG  
TTTCTGAAATCCCTGAAGGGGGTTGTACTGGGATTTGTGAATAAACTTGATACACCA

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**FIGURE 226**

MHLARLVGSCSLLLLLGALSGWAASDDPIEKVIEGINRGLSNAEREVGKALDGINSGITH  
AGREVEKVFENGLSNMGSHGTGKELDKGVQGLNHGMDKVAHEINHGIGQAGKEAEKLGHG  
VNNAAGQAGKEADKAVQGFHTGVHQAGKEAEKLGQGVNHAADQAGKEVEKLGQGAHHAAGQA  
GKELQNAHNGVNVQASKEANQLLNGNHQSGSSSHQGGATTTPLASGASVNTPFINLPALWR  
SVANIMP

**Important features of the protein:**

**Signal peptide:**

amino acids 1-25

**Homologous region to circumsporozoite (CS) repeats:**

amino acids 35-225

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**FIGURE 227**

GAAGTAGAGGTGTTGTGCTGAGCGGCGCTCGGCGAACTGTGTGGACCGTCTGCTGGGACT  
CCGGCCCTGCGTCCGCTCAGCCCCGTGGCCCCGCGCACCTACTGCCATGGAGACGCGGGCC  
TCGTCTCGGGGCCACCTGTTTGCTGGGCTTCAGTTTCCTGCTCCTCGTCATCTCTTCTGA  
TGGACATAATGGGCTTGGAAAGGGTTTTGGAGATCATATTCATTGGAGGACACTGGAAGA  
TGGGAAGAAAGAAGCAGCTGCCAGTGGACTGCCCCTGATGGTGATTATTCATAAATCCTG  
GTGTGGAGCTTGCAAAGCTCTAAAGCCCAAATTTGCAGAATCTACGGAAATTTCAGAACT  
CTCCCATAATTTTGTTATGGTAAATCTTGAGGATGAAGAGGAACCCAAAGATGAAGATTT  
CAGCCCTGACGGGGGTTATATTCACGAATCCTTTTTCTGGATCCCAGTGGCAAGGTGCA  
TCCTGAAATCATCAATGAGAATGGAAACCCAGCTACAAGTATTTTTATGTCAGTGCCGA  
GCAAGTTGTTCAGGGGATGAAGGAAGCTCAGGAAAGGCTGACGGGTGATGCCTTCAGAAA  
GAAACATCTTGAAGATGAATTGTAACATGAATGTGCCCCTTCTTTCATCAGAGTTAGTGT  
TCTGGAAGGAAAGCAGCAGGGAAGGGAATATTGAGGAATCATCTAGAACAATTAAGCCGA  
CCAGGAAACCTCATTCCTACCTACACTGGAAGGAGCGCTCTCACTGTGGAAGAGTTCTGC  
TAACAGAAGCTGGTCTGCATGTTTGTGGATCCAGCGGAGAGTGGCAGACTTTCTTCTCCT  
TTTCCCTCTCACCTAAATGTCAACTTGTCAATTGAATGTAAAGAATGAAACCTTCTGACAC  
AAAA

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## FIGURE 228

METRPRLGATCLLGFSFLLLVISSDGHNLGKGFGDHIHWRTLEDGKKEAAASGLPLMVI  
IHKSWCGACKALKPKFAESTEISELSHNFVMVNLEDEEPEKDEDFSPDGGYIPRILFLDP  
SGKVHPEIINENGNPYKYFYVSAEQVVQGMKEAQERLTGDAFRKKHLEDEL

Signal peptide:  
Amino acids 1-23

Thioredoxin family proteins Homology Block:  
Amino acids 58-75

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**FIGURE 229**

CCCACGCGTCCGCCCACGCGTCCGGGTGCCACTCGCGCGCCGGCCGCGCTCCGGGCTTCT  
CTTTTCCCTCCGACGCGCCACGGCTGCCCAGACATTCCGGCTGCCGGGTCTGGAGAGCTC  
CCCGAACCCTCCGCGGAGAGGAGCGAGGCGGCGCCAGGGTGGCCCCCGGGGCGCGCTTG  
GTCTCGGAGAAGCGGGGACGAGGCCGGAGGATGAGCGACTGAGGGCGACGCGGGCACTGA  
CGCGAGTTGGGGCCGCGACTACCGGCAGCTGACAGCGCGATGAGCGACTCCCCAGAGACG  
CCCTAGCCCAGGTGTGCGCGCCAGGCGGAGCGCGCAGGTGGGGCTGGGCTGTTAGTGGTCC  
GCCCCACGCGGGTCGCCCGCCGGCCCCAGGATGGGCGCTGGCAACCCGGGCCCCGCGCCCCG  
CGCTGCTACCCCTGCGCCCCGCTGCGAGCCCGGCGTCCGGCCCCGCGCCCTGCGCTCATGGA  
CGGCGGCTCCCGGCTGGCGGCGGCGCGCCCCCGGGCTGTGAATGCGACTCGCCCCCTCGGC  
CGCGCTCCCCGCCCCGCCGCCCGGGACGTGGTAGGGGATGCCAGCTCCACTGCGAT  
GGCAGTTGGCGCGCTCTCCAGTTCCCTCCTGGTCACTGCTGCCTGATGGTGGCTCTGTG  
CAGTCCGAGCATCCCGCTGGAGAAGCTGGCCCAGGCACCAGAGCAGCCGGGCCAGGAGAA  
GCGTGAGCACGCCACTCGGGACGGCCCCGGGGCGGGTGAACGAGCTCGGGCGCCCCGGCGAG  
GGACGAGGGCGGCAGCGGCCGGGACTGGAAGAGCAAGAGCGGCCGTGGGCTCGCCGGCCG  
TGAGCCGTGGAGCAAGCTGAAGCAGGCCTGGGTCTCCAGGGCGGGGGCGCCAAGGCCGG  
GGATCTGCAGGTCCGGCCCCGCGGGGACACCCCGCAGGCGGAAGCCCTGGCCGCAGCCGC  
CCAGGACGCGATTGGCCCCGGAACCTCGCGCCCACGCCCGAGCCACCCGAGGAGTACGTGTA  
CCCGGACTACCGTGGCAAGGGCTGCGTGGACGAGAGCGGCTTCGTGTACGCGATCGGGGA  
GAAGTTCGCGCCGGGCCCCCTCGGCCTGCCCGTGCCTGTGCACCGAGGAGGGGCGCTGTG  
CGCGCAGCCCGAGTGCCCGAGGCTGCACCCGCGCTGCATCCACGTCGACACGAGCCAGTG  
CTGCCCCGAGTGCAAGGAGAGGAAGAACTACTGCGAGTTCGGGGCAAGACCTATCAGAC  
TTTGGAGGAGTTCGTGGTGTCTCCATGCGAGAGGTGTCGCTGTGAAGCCAACGGTGAGGT  
GCTATGCACAGTGTGAGCGTGTCCCCAGACGGAGTGTGTGGACCCTGTGTACGAGCCTGA  
TCAGTGCTGTCCCATCTGCAAAAATGGTCCAAACTGCTTTGCAGAAACCGCGGTGATCCC  
TGCTGGCAGAGAAGTGAAGACTGACGAGTGCACCATATGCCACTGTACTTATGAGGAAGG  
CACATGGAGAATCGAGCGGCAGGCCATGTGCACGAGACATGAATGCAGGCAAATGTAGAC  
GCTTCCCAGAACACAAACTCTGACTTTTTCTAGAACATTTTACTGATGTGAACATTCTAG  
ATGACTCTGGGAACATCAGTCAAAGAAGACTTTTGATGAGGAATAATGGAAAATTGTTG  
GTACTTTTCTTTTCTTGATAACAGTTACTACAACAGAAGGAAATGGATATATTTCAAAA  
CATCAACAAGAACTTTGGGCATAAAATCCTTCTCTAAATAAATGTGCTATTTTACAGTA  
AGTACACAAAAGTACACTATTATATATCAAATGTATTTCTATAATCCCTCCATTAGAGAG  
CTTATATAAGTGTTTTCTATAGATGCAGATTAAAAATGCTGTGTTGTCAACCGTCAAAAA  
AAAAAAAAAAAAAAAAAAAAA



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**FIGURE 230**

MPSSTAMAVGALSSSLLVTCCLMVALCSPSIPLEKLAQAPEQPGQEKREHATRDGPGRVN  
ELGRPARDEGGSGRDWKSXSGRGLAGREPWSKLKQAWVSQGGGAKAGDLQVRPRGDTPOA  
EALAAAAQDAIGPELAPTPEPPPEEYVYPDYRGKGCVDSESGFVYAIGKFAFGPSACPCLC  
TEEGPLCAQPECPRHLHPRCIHVDTSQCCPQCKERKNYCEFRGKTYQTLEEFVVSPCERC  
CEANGEVLCTVSACPQTECVDPVYEPDQCCPICKNGPNCFAETAVIPAGREVKTDECTIC  
HCTYEEGTWRIERQAMCTRHECRQM

**Important features of the protein:****Signal peptide:**

amino acids 1-27

**Transmembrane domain:**

amino acids 11-30

**Glycosaminoglycan attachment site:**

amino acids 80-83

**N-myristoylation sites:**

amino acids 10-15, 102-107, 103-108

**Cell attachment sequence:**

amino acids 114-117

**EGF-like domain cysteine pattern signature:**

amino acids 176-187

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**FIGURE 231**

GGCCGGACGCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCCGCACGGAGGTTGTGAC  
CCCTACGGAGCCCCAGCTTGCCACGCACCCCACTCGGCGTCGCGCGGCGTGCCCTGCTT  
GTCACAGGTGGGAGGCTGGAACATCAGGCTGAAAAACAGAGTGGGTACTCTCTTCTGGG  
AAGCTGGCAACAAATGGATGATGTGATATATGCATTCCAGGGGAAGGGAATTGTGGTGC  
TTCTGAACCCATGGTCAATTAACGAGGCAGTTTCTAGCTACTGCACGTACTTCATAAAGC  
AGGACTCTAAAAGCTTTGGAATCATGGTGTCTGGAAGGGATTTACTTTTATACTGACTC  
TGTTTTGGGGAAGCTTTTTTGGGAAGCATTTCATGCTGAGTCCCTTTTTACCTTTGATGT  
TTGTAAACCCATCTTGGTATCGCTGGATCAACAACCGCCTTGTGGCAACATGGCTCACCC  
TACCTGTGGCATTATTGGAGACCATGTTTGGTGTAAAAGTGATTATAACTGGGGATGCAT  
TTGTTCCCTGGAGAAAGAAGTGTCAATTATCATGAACCATCGGACAAGAATGGACTGGATGT  
TCCTGTGGAATTGCCTGATGCGATATAGCTACCTCAGATTGGAGAAAAATTTGCCTCAAAG  
CGAGTCTCAAAGGTGTTCCCTGGATTGTTGGTGGGCCATGCAGGCTGCTGCCTATATCTTCA  
TTCATAGGAAATGGAAGGATGACAAGAGCCATTTTGAAGACATGATTGATTACTTTTGTG  
ATATTCACGAACCACTTCAACTCCTCATATTTCCAGAAGGGACTGATCTCACAGAAAACA  
GCAAGTCTCGAAGTAATGCATTTGCTGAAAAAAATGGACTTCAGAAATATGAATATGTTT  
TACATCCAAGAACTACAGGCTTTACTTTTGTGGTAGACCGTCTAAGAGAAGGTAAGAACC  
TTGATGCTGTCCATGATATCACTGTGGCGTATCCTCACAAACATTCCTCAATCAGAGAAGC  
ACCTCCTCCAAGGAGACTTTCCAGGGGAAATCCACTTTACGTCCACCGGTATCCAATAG  
ACACCTTCCCCACATCCAAGGAGGACCTTCAACTCTGGTGCCACAAACGGTGGGAAGAGA  
AAGAAGAGAGGCTGCGTTCCTTCTATCAAGGGGAGAAGAATTTTTATTTTACCGGACAGA  
GTGTCATTCCACCTTGCAAGTCTGAACTCAGGGTCCTTGTGGTCAAATTGCTCTCTATAC  
TGTATTGGACCCTGTTTCAAGCCCTGCAATGTGCCTACTCATATATTTGTACAGTCTTGTTA  
AGTGGTATTTTATAATCACCATTGTAATCTTTGTGCTGCAAGAGAGAATATTTGGTGGAC  
TGGAGATCATAGAACTTGCAATGTTACCGACTTTTACACAAACAGCCACATTTAAATTCAA  
AGAAAAATGAGTAAAGATTATAAGGTTTGCCATGTGAAAACCTAGAGCATATTTTGGAAT  
GTTCTAAACCTTTCTAAGCTCAGATGCATTTTGCATGACTATGTCGAATATTTCTTACT  
GCCATCATATTTTGTAAAGATATTTTGCATTAATTTTGTGGGAAAAATATTGCTACAA  
TTTTTTTTTAATCTCTGAATGTAATTTGATACTGTGTACATAGCAGGAGTGATCGGGGT  
GAAATAACTTGGGCCAGAATATTATTAAACAATCATCAGGCTTTTAAA

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**FIGURE 232**

MHSRGREIVVLLNPWSINEAVSSYCTYFIKQDSKSFSGIMVSWKGIYFILTLFWGSFFGSI  
FMLSPFLPLMFVNPSWYRWINNRLVATWLTLPVALLETMFGVKVIITGDAFVPGERSVII  
MNHRTMDWMFLWNCLMRYSYLRLEKICLKASLKGVPFGFWAMQAAAYIFIHRKWKDDKS  
HFEDMIDYFCDIHEPLQLLIFPEGTDLTENSKSRSNFAEKNGLQKYEYVLHPRTTGFTF  
VVDRLREGKNLDAVHDITVAYPHNIPQSEKHLQGDFFPREIHFHVHRYPIDTLPTSKEDL  
QLWCHKRWEEKERLRSFYQGEKNFYFTGQSVIPPCKSELRVLVVKLLSILYWTLFSPAM  
CLLIYLYSLVKWYFIITIVIFVLQERIFGGLEIELACYRLLHKQPHLNSKKNE

**Important features of the protein:**

**Signal peptide:**

amino acids 1-22

**Transmembrane domains:**

amino acids 44-63, 90-108, 354-377

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**FIGURE 233**

CGGCTCGAGTGCAGCTGTGGGGAGATTTCAAGTGCATTGCCTCCCCTGGGTGCTCTTCATC  
TTGGATTTGAAAAGTTGAGAGCAGCATGTTTTGCCCACTGAAACTCATCCTGCTGCCAGTG  
TTACTGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTTCCCGCCTGAGCTAACAGTC  
CATGTGGGTGATTCAAGCTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATA  
TTCAAGATAGACTGGACTCTGTCAACAGGAGAGCACGCCAAGGACGAATATGTGCTATAC  
TATTACTCCAATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGG  
GACATCTTATGCAATGATGGCTCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGA  
ACCTATATCTGTGAAATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTA  
CTGCATGTGCTTCCAGAGGAGCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTAG  
ATGGGATGTGTTTTCCAGAGCACAGAAGTGAACACGTGACCAAGGTAGAATGGATATTT  
TCAGGACGGCGCGCAAAGGAGGAGATTGTATTTGTTACTACCACAACTCAGGATGTCT  
GTGGAGTACTCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATT  
TTCCGCAATGACGGTTCCATCATGCTTCAAGGAGTGAGGGAGTCAGATGGAGGAACTAC  
ACCTGCAGTATCCACCTAGGGAACCTGGTGTTCAGAAAACCATTGTGCTGCATGTCAGC  
CCGGAAGAGCCTCGAACACTGGTGACCCCGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGT  
AATCAGTTGGTGATCATTGTGGGAATTGTCTGTGCCACAATCCTGCTGCTCCCTGTTCTG  
ATATTGATCGTGAAGAAGACCTGTGGAAATAAGAGTTCAGTGAATTCTACAGTCTTGGTG  
AAGAACACGAAGAAGACTAATCCAGAGATAAAAGAAAAACCCTGCCATTTTGAAGATGT  
GAAGGGGAGAAACACATTTACTCCCAATAATTGTACGGGAGGTGATCGAGGAAGAAGAA  
CCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCACCCAGTTTGGCCTTCTCTGAGG  
TCAGATCGGAACAACTCACTTGAAAAAAGTCAGGTGGGGGAATGCCAAAAACACAGCAA  
GCCTTTTGGAGAAGAATGGAGAGTCCCTTCATCTCAGCAGCGGTGGAGACTCTCTCCTGTG  
TGTGTCCTGGGCCACTCTACCAGTGATTTCAAGACTCCCGCTCTCCCAGCTGTCCTCCTGT  
CTCATTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGGCAGAGAGACTGGAC  
AGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGCCTCTGGAGTGGG  
ACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCCGTTGGATCAGACC  
CTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATAAAAACCAA  
CCCAAATCAA

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**FIGURE 234**

MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCI FKIDWTLS  
PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL  
KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE  
IVFRYYHKL RMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRES DGGNYTCSIHLGN  
LVFKKTI VLVHSPEEPRTLVT PAALRPLVLGGNQLV IIVGIVCATILLLPVLILIVKKTC  
GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPI IIVREVI EEEEPSEKSEAT  
YMTMHPVWPSLRSDRNNSLEKKSGGMPKTQQAF

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**FIGURE 235**

TAAACAGCTACAATATTCCAGGGCCAGTCACTTGCCATTTCTCATAACAGCGTCAGAGA  
GAAAGAACTGACTGAAACGTTTGAGATGAAGAAAGTTCTCCTCCTGATCACAGCCATCTT  
GGCAGTGGCTGTTGGTTTCCAGTCTCTCAAGACCAGGAACGAGAAAAAAGAAGTATCAG  
TGACAGCGATGAATTAGCTTCAGGGTTTTTTGTGTTCCCTTACCCATATCCATTTGCCCC  
ACTTCCACCAATTCCATTTCCAAGATTTCCATGGTTTAGACGTAATTTTCCTATTCCAAT  
ACCTGAATCTGCCCCCTACAACCTCCCCTTCCTAGCGAAAAGTAAACAAGAAGGATAAGTCA  
CGATAAACCTGGTCACCTGAAATTGAAATTGAGCCACTTCCTTGAAGAATCAAAATTCCT  
GTTAATAAAAGAAAAACAAATGTAATTGAAATAGCACACAGCATTTCTCTAGTCAATATCT  
TTAGTGATCTTCTTTAATAAACATGAAAGCAAAGATTTTGGTTTCTTAATTTCCACA

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## FIGURE 236

MKKVLLLLITAILAVAVGFPVSQDQEREKRSISDSDELASGFFVFPYPYPFRPLPPPIPFPR  
FPWFRRNFPIPIPIESAPTTPLPSEK

**Important features of the protein:**

**Signal peptide:**

amino acids 1-17

**Homologous region to B3-hordein:**

amino acids 47-85

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**FIGURE 237**

TCGCCATGGCCTCTGCCGGAATGCAGATCCTGGGAGTCGTCCTGACACTGCTGGGCTGGG  
TGAATGGCCTGGTCTCCTGTGCCCTGCCCATGTGGAAGGTGACCGCTTTCATCGGCAACA  
GCATCGTGGTGGCCCAGGTGGTGTGGGAGGGCCTGTGGATGTCTTGCGTGGTGCAGAGCA  
CCGGCCAGATGCAGTGCAAGGTGTACGACTCACTGCTGGCGCTGCCACAGGACCTGCAGG  
CTGCACGTGCCCTCTGTGTTCATCGCCCTCCTTGTGGCCCTGTTGCGCTTGCTGGTCTACC  
TTGCTGGGGCCAAGTGTACCACCTGTGTGGAGGAGAAGGATTCCAAGGCCCGCCTGGTGC  
TCACCTCTGGGATTGTCTTTGTTCATCTCAGGGGTCCTGACGCTAATCCCCGTGTGCTGGA  
CGGCGCATGCCATCATCCGGGACTTCTATAACCCCCCTGGTGGCTGAGGCCCAAAAGCGGG  
AGCTGGGGGCCTCCCTCTACTTGGGCTGGGCGGCCTCAGGCCTTTTGTGCTGGGTGGGG  
GGTTGCTGTGCTGCACTTGCCCCCTCGGGGGGGTCCCAGGGCCCCAGCCATTACATGGCCC  
GCTACTCAACATCTGCCCCCTGCCATCTCTCGGGGGCCCTCTGAGTACCCTACCAAGAATT  
ACGTCTGACGTGGAGGGGAATGGGGGCTCCGCTGGCGCTAGAGCCATCCAGAAGTGGCAG  
TGCCCAACAGCTTTGGGATGGGTTTCGTACCTTTTGTCTTGCTCCTGCTATTTTTCTTT  
TGACTGAGGATATTTAAAAATTCATTTGAAAACTGAGCCAAGGTGTTGACTCAGACTCTCA  
CTTAGGCTCTGCTGTTTTCTCACCCTTGATGATGGAGCCAAAGAGGGGATGCTTTGAGAT  
TCTGGATCTTGACATGCCCATCTTAGAAGCCAGTCAAGCTATGGAACATAATGCGGAGGCT  
GCTTGCTGTGCTGGCTTTGCAACAAGACAGACTGTCCCCAAGAGTTCCTGCTGCTGCTGG  
GGGCTGGGCTTCCCTAGATGTCACTGGACAGCTGCCCCCATCCTACTCAGGTCTCTGGA  
GCTCCTCTCTTCACCCCTGGAAAAACAAATCATCTGTAAACAAAGGACTGCCCACCTCCG  
GAACTTCTGACCTCTGTTTCCTCCGTCTGATAAGACGTCCACCCCCCAGGGCCAGGTCC  
CAGCTATGTAGACCCCCGCCCCACCTCCAACACTGCACCCTTCTGCCCTGCCCCCTCG  
TCTCACCCCTTTTACACTCACATTTTTTATCAAATAAAGCATGTTTTGTTAGTGCA



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**FIGURE 238**

MASAGMQILGVVLTLLGWVNGLVSCALPMWKVTAFIGNSIVVAQVVWEGWLMSCVVQSTG  
QMCKVYDSLALPQDLQAARALCVIALLVALLFGLLVYLAGAKCTTCVEEKDSKARLVLT  
SGIVFVISGVLTLIPVCWTAHAIIRDFYNPLVAEAQKRELGASLYLGWAASGLLLLGGGL  
LCCTCPSGGSQGPPSHYMARYSTSAPAISRGPPSEYPTKNYV

**Transmembrane domains:**

amino acids 8-30 (type II), 82-102, 121-140, 166-186

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**FIGURE 239**

AGTGACAATCTCAGAGCAGCTTCTACACCACAGCCATTTCCAGCATGAAGATCACTGGGG  
GTCTCCTTCTGCTCTGTACAGTGGTCTATTTCTGTAGCAGCTCAGAAGCTGCTAGTCTGT  
CTCCAAAAAAGTGGACTGCAGCATTTACAAGAAGTATCCAGTGGTGGCCATCCCCTGCC  
CCATCACATACCTACCAGTTTGTGGTTCTGACTACATCACCTATGGGAATGAATGTCACT  
TGTGTACCGAGAGCTTGAAAAGTAATGGAAGAGTTCAGTTTCTTCACGATGGAAGTTGCT  
AAATTCTCCATGGACATAGAGAGAAAGGAATGATATTCTCATCATCATCTTCATCATCCC  
AGGCTCTGACTGAGTTTCTTTCAGTTTACTGATGTTCTGGGTGGGGGACAGAGCCAGAT  
TCAGAGTAATCTTGACTGAATGGAGAAAGTTTCTGTGCTACCCCTACAAACCCATGCCTC  
ACTGACAGACCAGCATTTTTTTTTTAACACGTCAATAAAAAAATAATCTCCCAGA

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## FIGURE 240

MKITGGLLLLCTVVYFCSSSEAASLSPKKVDCSIYKKYPVVAIPCPITYLPVCGSDYITY  
GNECHLCTESLKSNGRVQFLHDGSC

**Signal peptide:**  
amino acids 1-19

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**FIGURE 241**

CCCGCGCCCGGTTCTCCCTCGCAGCACCTCGAAGTGC GCCCCTCGCCCTCCTGCTCGCGC  
CCCGCCGCCATGGCTGCCTCCCCGCGCGGCCTGCTGTCCTGGCCCTGACCGGGCTGGCG  
CTGCTCCTGCTCCTGTGCTGGGGCCCAGGTGGCATAAGTGGAAATAAACTCAAGCTGATG  
CTTCAAAAACGAGAAGCACCTGTTCCAAC TAAGTAAAGTGGCCGTTGATGAGAATAAA  
GCCAAAGAATTCTTTGGCAGCCTGAAGCGCCAGAAGCGGCAGCTGTGGGACCGGACTCGG  
CCCGAGGTGCAGCAGTGGTACCAGCAGTTTCTCTACATGGGCTTTGATGAAGCGAAATTT  
GAAGATGACATCACCTATTGGCTTAACAGAGATCGAAATGGACATGAATACTATGGCGAT  
TACTACCAACGTCACTATGATGAAGACTCTGCAATTGGTCCCCGGAGCCCCTACGGCTTT  
AGGCATGGAGCCAGCGTCAACTACGATGACTACTTAACCATGACTTGCCACACGCTGTACA  
AGAAGCAAATAGCGATTCTCTTCATGTATCTCCTAATGCCTTACACTACTTGGTTTCTGA  
TTTGCTCTATTTTCAGCAGATCTTTTCTACCTACTTTGTGTGATCAAAAAAGAAGAGTTAA  
AACAAACACATGTAAATGCCTTTTGATATTTTCATGGGAATGCCTCTCATTTAAAAATAGAA  
ATAAAGCATTTTGT TAAAAAGA

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**FIGURE 242**

MAASPARPAVLALTGLALLLLLCWGPGGISGNKLKMLQKREAPVPTKTKVAVDENKAKE  
FLGSLKRQKRQLWDRTRPEVQQWYQQFLYMGFDEAKFEDDITYWLNDRDRNGHEYYGDYYQ  
RHYEDSAIGPRSPYGFRHGASVNYDDY

**Signal peptide:**  
amino acids 1-30

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**FIGURE 243**

CTCCATTAAACCACCACCAGCTCCCCAAGCCACCCCTTCAGCCATGAAGTTCCTGCTCCT  
GGTCTTGGCAGCCCTCGGATTCTTGACCCAGGTGATCCCAGCCAGTGCAGGTGGGTCAAA  
ATGTGTGAGTAACACCCAGGATACTGCAGGACATGTTGCCACTGGGGGAGACAGCATT  
GTTTCATGTGCAACGCTTCCAGAAAATGCTGCATCAGCTACTCCTTCCTGCCGAAGCCTGA  
CCTACCACAGCTCATCGGTAACCACTGGCAATCAAGGAGAAGAAACACACAAAGGAAAGA  
CAAGAAGCAACAAACGACCGTAACATCATATAAACCCTGCTATCGCCTCCACCAACTCA  
GAGAAATATCATTTCCACAGTTCCAATTCTCTACATTGCTGAGTACTAGCCAAGGCTC  
CTCTTTTATGGGGCAGATATCTATAGCCAACCCCAAACTTCTGTCTTCTATCATTCTGTC  
ATTCATCTAGTAACTAATTTGGAGTTTGTATCTATCTTACGAGAACAATCATCATGCAGA  
TTCGTCCACAGGGGATCTGTGAGTTTGGGTCTCCAAATGAAAAATGTCAAGACAGAATT  
GGACATGCAAAAGATTGACTGGGAGAACACACCTCTGATGGACAAAGGTGAGACAGAGCA  
GCCACAGGCAGGGAGAGCCTTCAGACTGCAACGCTGGCCTGATACGTGTCAAAGGAGAGA  
GGGATAGAGGAGGATTGAATAGAAGGAGACTAAGACTGCAGCTCTAAGAAAGTCTCAGCC  
AAACAGATGGGGAGGCCCAAAGCAAGGCTTGCCCTCAGAGGAGCTCACGCAGGGCAGGA  
ATAGCCAGGTTCTCATATCCCAGGGGTTTCAGACTTGGCTGAGAACAGCCCCCTGGAGAACA  
TGGGGTGACTGCTACCATAGGTCTGGAAGTATGAGGCTGTCCACCAACTATCCCCTTGAA  
GCAAGTTCTCTTGAAAGGAAATCTAAACAGTGCACCCCCATGGCTGCCACGGAGTATAAG  
GAGGGAGAGAAAGGAGCTGAAAGTCTAGGTTTGGCCAGCTAGGTAGACTGACTTGTGAGG  
TATTTATTTATTCATTTGAGTAACAAAGCAGACAGAATACATAGCCACCATTGGTAGTAC  
ACCCCAAAAGCAAGGATGGCATGATGCTGGTGACTCAAACGTGCCTACTCATGGTGTCAA  
ATTGGCATAATCCTCTTGGAAGCTGTGTGGAATAAGCACAGAGAAGCAGAACTCTAAT  
TGCTTAATCCACTAAACATTACTTCTGGAATTGGCTCATCATAAATTATCCAAGAGAAA  
GCACAAAGTTATGGGCACAAAGGTTTTCCATATAATATTATTTAAATGCTGAGAAAATG  
AAAAAATCTAAATGGTGAAATATATACTAATGCCATCTATAAATACAAACAAATAGAATG  
TTTATAGAATAATGGAACATAATAACATTATTCAAATGCAATTTATGCTATAGTTGTCA  
AAATTGTCTCCTTATATGATACAAACTCATGAAATTATGACTTTTTTGTGTTGGTTGGA  
AAGCAGAATTATGCATAAATTTCTCTTACAGTTCGATGCCATTAGTTTTATATAACAT  
TTATTTGACACGTA CTGACTTCTATCTGAGAAGAACAAACCAAAACACTCAGGCCTAAT  
AATTAAAAACGGTCCATAAAACTAGCAAACCAGATAAGAAAAGATGTTAATGCCCATTC  
CTAACTTATGTCTTAGACCAAATTAATTCTAGATGGTTTTAAATGACAGTGTAAGT  
AAAGTATTAAAAGATTGTGTGGTCAAATATTCAATTTAAGAGCAAGGAAATCTTATAAA  
TATAACAATAGAGGCAGAACTCATGTAAGAATAAATTGATTAGGTGGTATTAAATATTAA  
GTTCTTATGTATGTCAAAGATATCATTTTGAATTCATCCATCTTATTGGGTATTGCAG  
GAGTTCATTCTTTTTTGTGTTATAAATACTCTCCGTCATATGAATAGTATTCAATTTGTAT  
ACTGGTTTGTGATGGACATTGGGTTGTTCCAGTTTATGGCTATTACAAATAAGCTT  
CTATGAACATTTATGTACA

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**FIGURE 244**

MKFLLLVLAALGFLTQVIPASAGGSKCVSNTPGYCRTCCCHWGETALFMCNASRKCCISYS  
FLPKPDLPLQLIGNHWQSRRRNTQRKDKKQQTTVTS

**Important features of the protein:**

**Signal peptide:**

amino acids 1-16

**Transmembrane domain:**

amino acids 1-22

**N-glycosylation site:**

amino acids 50-53

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 79-82

**N-myristoylation site:**

amino acids 23-28

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**FIGURE 245**

GGAGAGAGGCGCGCGGGTGAAAGGCGCATTGATGCAGCCTGCGGCGGCCTCGGAGCGCGG  
CGGAGCCAGACGCTGACCACGTTCTCTCCTCGGTCTCCTCCGCCTCCAGCTCCGCGCTG  
CCCGGCAGCCGGGAGCCATGCGACCCAGGGCCCCGCCGCTCCCCGCAGCGGCTCCGCG  
GCCTCCTGCTGCTCCTGCTGCTGCAGCTGCCCGCGCCGTCGAGCGCCTCTGAGATCCCCA  
AGGGGAAGCAAAAGGCGCAGCTCCGGCAGAGGGAGGTGGTGGACCTGTATAATGGAATGT  
GCTTACAAGGGCCAGCAGGAGTGCCTGGTCGAGACGGGAGCCCTGGGGCCAATGTTATTC  
CGGGTACACCTGGGATCCCAGGTCCGGATGGATTCAAAGGAGAAAAGGGGGAATGTCTGA  
GGGAAAGCTTTGAGGAGTCCTGGACACCCAACTACAAGCAGTGTTTATGGAGTTCATTGA  
ATTATGGCATAGATCTTGGGAAAATTGCGGAGTGTACATTTACAAAGATGCGTTCAAATA  
GTGCTCTAAGAGTTTTGTTTCAAGTGGCTCACTTCGGCTAAAATGCAGAAATGCATGCTGTC  
AGCGTTGGTATTTTACATTCAATGGAGCTGAATGTTTCAAGACCTCTTCCCATTGAAGCTA  
TAATTTATTTGGACCAAGGAAGCCCTGAAATGAATTTCAACAATTAATATTCATCGCACTT  
CTTCTGTGGAAGGACTTTGTGAAGGAATTGGTGTGATTAGTGGATGTTGCTATCTGGG  
TTGGCACTTGTTTCAAGATTACCCAAAAGGAGATGCTTCTACTGGATGGAATTCAGTTTCTC  
GCATCATTATTGAAGAACTACCAAAATAAATGCTTTAATTTTCAATTTGCTACCTCTTTTT  
TTATTATGCCTTGGAATGGTTTCACTTAAATGACATTTTAAATAAGTTTATGTATACATCT  
GAATGAAAAGCAAAGCTAAATATGTTTACAGACCAAAGTGTGATTTCACTGTTTTTAA  
ATCTAGCATTATTCATTTTGCTTCAATCAAAGTGGTTTCAATATTTTTTTTAGTTGGTT  
AGAATACTTTCTTCATAGTCACATTCTCTCAACCTATAATTTGGAATATTGTTGTGGTCT  
TTTGTTTTTTCTCTTAGTATAGCATTTTTTAAAAAATATAAAAGCTACCAATCTTTGTAC  
AATTTGTAAATGTTAAGAATTTTTTTTATATCTGTTAAATAAAAATTATTTCCAACA



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**FIGURE 246**

MRPQGPAASPQRLRGLLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPA  
GVPGRDGSPGANVIPGTPGIPGRDGFKEKGECLRESFEESWTPNYKQCSWSSLNYGIDL  
GKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIYLDQ  
GSPEMNSTINIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIEE  
LPK

**Signal peptide:**  
amino acids 1-30

**Transmembrane domain:**  
amino acids 195-217

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**FIGURE 247**

GGCCGTTGGTTGGTGCGCGGCTGAAGGGTGTGGCGCGAGCAGCGTCGTTGGTTGGCCGGC  
GGCGGGCCGGGACGGGCATGGCCCTGCTGCTGTGCCTGGTGTGCCTGACGGCGGCGCTGG  
CCCACGGCTGTCTGCACTGCCACAGCAACTTCTCCAAGAAGTTCTCCTTCTACCGCCACC  
ATGTGAACTTCAAGTCTTGGTGGGTGGGCGACATCCCCGTGTCAGGGGCGCTGCTCACC  
ACTGGAGCGACGACACGATGAAGGAGCTGCACCTGGCCATCCCCGCCAAGATCACCCGGG  
AGAAGCTGGACCAAGTGGCGACAGCAGTGTACCAGATGATGGATCAGCTGTACCAGGGGA  
AGATGTACTTCCCCGGGTATTTCCCCAACGAGCTGCGAAACATCTTCCGGGAGCAGGTGC  
ACCTCATCCAGAACGCCATCATCGAAAGGCACCTGGCACCAGGCAGCTGGGGAGGAGGGC  
AGCTCTCCAGGGAGGGACCCAGCCTAGCACCTGAAGGATCAATGCCATCACCCCGCGGGG  
ACCTCCCCTAAGTAGCCCCCAGAGGCGCTGGGAGTGTGCCACCGCCCTCCCTGAAGTT  
TGCTCCATCTCACGCTGGGGGTCAACCTGGGGACCCCTTCCCTCCGGGCCATGGACACAC  
ATACATGAAAACCAGGCCGCATCGACTGTGACACCGCTGTGGCATCTTCCAGTACGAGA  
CCATCTCCTGCAACAACTGCACAGACTCGCACGTGCGCTGCTTTGGCTATAACTGCGAGT  
AGGGCTCAGGCATCACACCCACCCGTGCCAGGGCCCTACTGTCCCTGGGGTCCCAGGCTC  
TCCTTGAGGGGGCTCCCCGCTTCCACCTGGCTGTCATCGGGTAGGGCGGGGCCGTGGG  
TTCAGGGGCGCACCACTTCCAAGCCTGTGTCCACAGGTCCTCGGCGCAGTGGAAGTCAG  
CTGTCCAGGGCCTCCTGAACTACATAAATAACTGGCACAAGTAAGTCCCTCCTCAAACC  
AACACAGGCAGTGTGTGTATGTGAGCACCTCGTGGGTGAGTATGTGTGGGGCACAGGCTG  
GCTCCCTCAGCTCCACGTCCTAGAGGGGCTCCCGAGGAGGTGGAACCTCAACCCAGCTC  
TGCGCAGGAGGCGGCTGCAGTCCTTTTCTCCCTCAAAGGTCTCCGACCTCAGCTGGAGG  
CGGGCATCTTTCCTAAAGGGTCCCCATAGGGTCTGGTTCCACCCCATCCCAGGTCTGTGG  
TCAGAGCCTGGGAGGGTTCCCTACGATGGTTAGGGGTGCCCCATGGAGGGGCTGACTGCC  
CCACATTGCCCTTTCAGACAGGACACGAGCATGAGGTAAGGCCGCCCTGACCTGGACTTCA  
GGGGGAGGGGGTAAAGGGAGAGAGGAGGGGGGCTAGGGGGTCTCTAGATCAGTGGGGG  
ACTGCAGGTGGGGCTCTCCCTATACCTGGGACACCTGCTGGATGTACCTCTGCAACCAC  
ACCCATGTGGTGGTTTCATGAACAGACCACGCTCCTCTGCCTTCTCCTGGCCTGGGACAC  
ACAGAGCCACCCCGCCTTGTGAGTGACCCAGAGAAGGGAGGCCCTCGGGAGAAGGGGTGC  
TCGTAAGCCAACACCAGCGTGCCGCGGCCTGCACACCCTTCGGACATCCCAGGCACGAGG  
GTGTGCTGGATGTGGCCACACATAGGACCACACGTCCAGCTGGGAGGAGAGGCTGGGG  
CCCCCAGGGAGGGAGGCAGGGGGTGGGGGACATGGAGAGCTGAGGCAGCCTCGTCTCCCC  
GCAGCCTGGTATCGCCAGCCTTAAGGTGTCTGGAGCCCCCACACTTGGCCAACCTGACCT  
TGGAAGATGCTGCTGAGTGTCTCAAGCAGCACTGACAGCAGCTGGGCCTGCCCCAGGGCA  
ACGTGGGGGCGGAGACTCAGCTGGACAGCCCCTGCCTGTCACTCTGGAGCTGGGCTGCTG  
CTGCCTCAGGACCCCTCTCCGACCCCGGACAGAGCTGAGCTGGCCAGGGCCAGGAGGGC  
GGGAGGGAGGGAATGGGGGTGGGCTGTGCGCAGCATCAGCGCCTGGGCAGGTCCGCAGAG  
CTGCGGGATGTGATTAAAGTCCCTGATGTTTCTC

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## FIGURE 248

MALLLCLVCLTAALAHGCLHCHSNFSKKFSFYRHHVNFKSWWVGDI PVSGALLTDWSDDT  
MKELHLAIPAKITREKLDQVATAVYQMMDQLYQGKMYFFPGYFPNELRNIFREQVHLIQNA  
IIERHLAPGSWGGGQLSREGPSLAPEGSMPSPRGDLP

**Signal peptide:**  
amino acids 1-15

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**FIGURE 249**

CGACGATGCTACGCGCGCCCGGCTGCCTCCTCCGGACCTCCGTAGCGCCTGCCGCGGCC  
TGGCTGCGGCGCTGCTCTCGTCGCTTGCGCGCTGCTCTCTTCTAGAGCCGAGGGACCCGG  
TGGCCTCGTCGCTCAGCCCCCTATTTTCGGCACCAAGACTCGCTACGAGGATGTCAACCCCG  
TGCTATTGTGCGGGCCCCGAGGCTCCGTGGCGGGACCCCTGAGCTGCTGGAGGGGACCTGCA  
CCCCGGTGCAGCTGGTCGCCCTCATTTCGCCACGGCACCCGCTACCCACGGTCAAACAGA  
TCCGCAAGCTGAGGCAGCTGCACGGGTTGCTGCAGGCCCGCGGGTCCAGGGATGGCGGGG  
CTAGTAGTACCGGCAGCCGCGACCTGGGTGCAGCGCTGGCCGACTGGCCTTTGTGGTACG  
CGGACTGGATGGACGGGCAGCTAGTAGAGAAGGGACGGCAGGATATGCGACAGCTGGCGC  
TGCGTCTGGCCTCGCTCTTCCCGGCCCTTTTCAGCCGTGAGAACTACGGCCGCCTGCGGC  
TCATCACCAGTTCCAAGCACCGCTGCATGGATAGCAGCGCCGCCTTCTGCAAGGGCTGT  
GGCAGCACTACCACCCTGGCTTGCCGCCGCCGGACGTGCGAGATATGGAGTTTGGACCTC  
CAACAGTTAATGATAAACTAATGAGATTTTTTGATCACTGTGAGAAGTTTTTAACTGAAG  
TAGAAAAAATGCTACAGCTCTTTATCACGTGGAAGCCTTCAAACTGGACCAGAAATGC  
AGAACATTTTAAAAAAGTTGCAGCTACTTTGCAAGTGCCAGTAAATGATTTAAATGCAG  
ATTTAATTCAAGTAGCCTTTTTTCACTGTTCATTTGACCTGGCAATTAAAGGTGTAAAT  
CTCCTTGGTGTGATGTTTTTGACATAGATGATGCAAAGGTATTAGAATATTTAAATGATC  
TGAAACAATATTGGAAAAGAGGATATGGGTATACTATTAACAGTCGATCCAGCTGCACCT  
TGTTTCAGGATATCTTTTCAGCACTTGGACAAAGCAGTTGAACAGAAACAAAGGTCTCAGC  
CAATTTCTTCTCCAGTCATCCTCCAGTTTGGTCATGCAGAGACTCTTCTTCCACTGCTTT  
CTCTCATGGGCTACTTCAAAGACAAGGAACCCCTAACAGCGTACAATTACAAAAACAAA  
TGCATCGGAAGTTCCGAAGTGGTCTCATTGTACCTTATGCCTCGAACCTGATATTTGTGC  
TTTACCCTGTGAAAATGCTAAGACTCCTAAAGAACAATTCCGAGTGCAGATGTTATTAA  
ATGAAAAGGTGTTACCTTTGGCTTACTCACAAGAACTGTTTCATTTTATGAAGATCTGA  
AGAACCCTACAAGGACATCCTTCAGAGTTGTCAAACCAGTGAAGAATGTGAATTAGCAA  
GGGCTAACAGTACATCTGATGAACATGAGTAAGTGAAGAACATTTTTAATTCTTTAGGA  
ATCTGCAATGAGTGATTACATGCTTGTAATAGGTAGGCAATTCCTTGATTACAGGAAGCT  
TTTATATTACTTGAGTATTTCTGTCTTTTACAGAAAAACATTGGGTTTCTCTCTGGGTT  
TGGACATGAAATGTAAGAAAAGATTTTTTCACTGGAGCAGCTCTCTTAAGGAGAAACAAAT  
CTATTTAGAGAAACAGCTGGCCCTGCAAATGTTTACAGAAATGAAATTCTTCTACTTAT  
ATAAGAAATCTCACACTGAGATAGAATTGTGATTTTATAATAACACTTGAAAAGTGCTGG  
AGTAACAAAATATCTCAGTTGGACCATCCTTAACCTTGATTGAACTGTCTAGGAACCTTAC  
AGATTGTTCTGCAGTTCTCTCTTCTTTTCTCAGGTAGGACAGCTCTAGCATTTTCTTAA  
TCAGGAATATTGTGGTAAGCTGGGAGTATCACTCTGGAAGAAAGTAACATCTCCAGATGA  
GAATTTGAAACAAGAAACAGAGTGTGTAAAAGGACACCTTCACTGAAGCAAGTCGGAAA  
GTACAATGAAAATAAATATTTTTGGTATTTATTTATGAAATATTTGAACATTTTTTCAAT  
AATTCCTTTTTTACTTCTAGGAAGTCTCAAAGACCATCTTAAATTATTATATGTTTGGAC  
AATTAGCAACAAGTCAGATAGTTAGAATCGAAGTTTTTCAAATCCATTGCTTAGCTAACT  
TTTTCACTCTGTCACTTGGCTTCGATTTTTATATTTTCTATTATATGAAATGTATCTTT  
TGGTTGTTTGATTTTTCTTCTTTCTTTGTAAATAGTTCTGAGTTCTGTCAAATGCCGTG  
AAAGTATTTGCTATAATAAAGAAAATTCTTGTGACTTTAAAAA

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**FIGURE 250**

MLRAPGCLLR TSVAPAAALAAALLSSLARCSLLEPRDPVASSLS PYFGTKTRYEDVNPVL  
LSGPEAPWRDPELLEGTCTPVQLVALIRHGTRYPTVKQIRKLRQLHGLLQARGSRDGGAS  
STGSRDLGAALADWPLWYADWMDGQLVEKGRQDMRQLALRLASLFPALFSRENYGRLRLI  
TSSKHRCMDSSAAFLQGLWQHYHPGLPPPVDADMEFGPPTVNDKLMRFFDHCEKFLTEVE  
KNATALYHVEAFKTGPENILKKVAATLQVPVNDLNADLIQVAFFTC SFDLAIKGVKSP  
WCDVFDIDDAKVLEYLNDLKQYWKRGYGYTTINSRSSCTLFQDIFQHLDKAVEQKQRSQPI  
SSPVILQFGHAETLLPLLSLMGYFKDKEPLTAYNYKKQMHRKFRSGLIVPYASNLI FVLY  
HCENAKTPKEQFRVQMLLNEKVLPLAYSQETVSFYEDLKNHYKDILQSCQTSEECELARA  
NSTSDEL

**Important features:****Signal sequence**

amino acids 1-30

**N-glycosylation sites:**

amino acids 242-246, 481-485

**N-myristoylation sites.**

amino acids 107-113, 113-119, 117-123, 118-124, 128-134

**Endoplasmic reticulum targeting sequence:**

amino acids 484-489

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**FIGURE 251**

GGAGAGCCGCGGCTGGACACCGAGTGGGGAGCGCGGCTGGAGGTGCCACCCGGCGCGGG  
TGGCGGAGAGATCAGAAGCCTCTTCCCCAAGCCGAGCCAACCTCAGCGGGGACCCGGGGCT  
CAGGGACGCGGCGGCGGCGGCGGCGACTGCAGTGGCTGGACGATGGCAGCGTCCGCCGGA  
GCCGGGGCGGTGATTGCAGCCCCAGACAGCCGGCGCTGGCTGTGGTTCGGTGTCTGGCGGCG  
GCGCTTGGGCTCTTGACAGCTGGAGTATCAGCCTTGGAAGTATATACGCCAAAAGAAATC  
TTCGTGGCAAATGGTACACAAGGGAAGCTGACCTGCAAGTTCAAGTCTACTAGTACGACT  
GGCGGGTTGACCTCAGTCTCCTGGAGCTTCCAGCCAGAGGGGGCCGACACTACTGTGTCTG  
TTTTTCCACTACTCCCAAGGGCAAGTGTACCTTGGGAATTATCCACCATTTAAAGACAGA  
ATCAGCTGGGCTGGAGACCTTGACAAGAAAGATGCATCAATCAACATAGAAAATATGCAG  
TTTATACACAATGGCACCTATATCTGTGATGTCAAAAACCTCCTGACATCGTTGTCCAG  
CCTGGACACATTAGGCTCTATGTCTGTAGAAAAAGAGAATTTGCCTGTGTTTCCAGTTTGG  
GTAGTGGTGGGCATAGTTACTGCTGTGGTTCCTAGGTCTCACTCTGCTCATCAGCATGATT  
CTGGCTGTCTCTATAGAAGGAAAACTCTAAACGGGATTACACTGGCTGCAGTACATCA  
GAGAGTTTGTCACCAGTTAAGCAGGCTCCTCGGAAGTCCCCCTCCGACACTGAGGGTCTT  
GTAAAGAGTCTGCCTTCTGGATCTCACCAGGGCCCAGTCATATATGCACAGTTAGACCAC  
TCCGGCGGACATCACAGTGACAAGATTAACAAGTCAGAGTCTGTGGTGTATGCGGATATC  
CGAAAGAATTAAAGAGAATACCTAGAACATATCCTCAGCAAGAAACAAAACCAAACCTGGAC  
TCTCGTGCAGAAAATGTAGCCCATTAACCATGTAGCCTTGGAGACCCAGGCAAGGACAA  
GTACACGTGTACTCACAGAGGGAGAGAAAGATGTGTACAAAGGATATGTATAAATATTCT  
ATTTAGTCATCCTGATATGAGGAGCCAGTGTTCATGATGAAAAGATGGTATGATTCTAC  
ATATGTACCCATTGTCTTGCTGTTTTTGTACTTTCTTTTCAGGTCAATTACAAATTGGGAG  
ATTTCAGAAACATTCTTTTACCATCATTAGAAATGGTTTGCCTTAATGGAGACAATAG  
CAGATCCTGTAGTATTTCCAGTAGACATGGCCTTTTAAATCTAAGGGCTTAAGACTGATTA  
GTCTTAGCATTTACTGTAGTTGGAGGATGGAGATGCTATGATGGAAGCATAACCCAGGGTG  
GCCTTTAGCACAGTATCAGTACCATTTATTTGTCTGCCGCTTTTAAAAAATACCCATTGG  
CTATGCCACTTGAAAACAATTTGAGAAGTTTTTTTTGAAGTTTTTCTACTAAAATATGGG  
GCAATTGTTAGCCTTACATGTTGTGTAGACTTACTTTAAGTTTTCACCCCTTGAAATGTGT  
CATATCAATTTCTGGATTCAATAAGATTAGCAAAGGATAAATGCCGAAGGTCACT  
TCATTCTGGACACAGTTGGATCAATACTGATTAAGTAGAAAATCCAAGCTTTGCTTGAGA  
ACTTTTTGTAACGTGGAGAGTAAAAAGTATCGGTTTTTA

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**FIGURE 252**

MAASAGAGAVIAAPDSRRWLWSVLAAALGLLTAGVSALEVYTPKEIFVANGTQGKLTCKF  
KSTSTTGGLTSVSWSFQPEGADTTVSFFHYSQGQVYLGNYPPFKDRISWAGDLDDKSDASI  
NIENMQFIHNGTYICDVKNPPDIVVQPGHIRLYVVEKENLPVFPVWVVVGIVTAVVLGLT  
LLISMILAVLYRRKNSKRDTGCGSTSESLSPVKQAPRKSPSDTEGLVKSLPSGSHQGPVI  
YAQLDHSGGHHSDKINKSESVVYADIRKN

**Signal peptide:**  
amino acids 1-37

**Transmembrane domain:**  
amino acids 161-183

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**FIGURE 253**

GTGACACTATAGAAGAGCTATGACGTCGCATGCACGCGTACGTAAGCTCGGAATTCGGCT  
CGAGGCTGGTGGGAAGAAGCCGAGATGGCGGCAGCCAGCGCTGGGGCAACCCGGCTGCTC  
CTGCTCTTGCTGATGGCGGTAGCAGCGCCAGTCGAGCCCGGGGCAGCGGCTGCCGGGCC  
GGGACTGGTGC GCGAGGGGCTGGGGCGGAAGGTCGAGAGGGCGAGGCCTGTGGCACGGTG  
GGGCTGCTGCTGGAGCACTCATTTGAGATCGATGACAGTGCCAACCTCCGGAAGCGGGGC  
TCACTGCTCTGGAACCAGCAGGATGGTACCTTGTCCCTGTCACAGCGGCAGCTCAGCGAG  
GAGGAGCGGGGCCGACTCCGGGATGTGGCAGCCCTGAATGGCCTGTACCGGGTCCGGATC  
CCAAGGCGACCCGGGGCCCTGGATGGCCTGGAAGCTGGTGGCTATGTCTCCTCCTTTGTC  
CCTGCGTGCTCCCTGGTGGAGTCGCACCTGTTCGGACCAGCTGACCCTGCACGTGGATGTG  
GCCGGCAACGTGGTGGGCGTGTTCGGTGGTGACGCACCCCGGGGGCTGCCGGGGCCATGAG  
GTGGAGGACGTGGACCTGGAGCTGTTCAACACCTCGGTGCAGCTGCAGCCGCCACCACA  
GCCCCAGGCCCTGAGACGGCGGCCTTCATTGAGCGCCTGGAGATGGAAACAGGCCCCAGAAG  
GCCAAGAACCCCCAGGAGCAGAAGTCCTTCTTCGCCAAATACTGGATGTACATCATTCCC  
GTCGTCCTGTTCTCATGATGTCAGGAGCGCCAGACACCGGGGGCCAGGGTGGGGGTGGG  
GGTGGGGGTGGTGGTGGGGGTAGTGGCCTTTGCTGTGTGCCACCCTCCCTGTAAAGTCTAT  
TTAAAAACATCGACGATACATTGAAATGTGTGAACGTTTTGAAAAGCTACAGCTTCCAGC  
AGCCAAAAGCAACTGTTGTTTTGGCAAGACGGTCCTGATGTACAAGCTTGATTGAAATTC  
ACTGCTCACTTGATACGTTATTCAGAAACCCAAGGAATGGCTGTCCCCATCCTCATGTGG  
CTGTGTGGAGCTCAGCTGTGTTGTGTGGCAGTTTATTAACTGTCCCCCAGATCGACACG  
CAAAAAAAAA



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**FIGURE 254**

MAAASAGATRLLLLLLMAVAAPSRARGSGCRAGTGARGAGAEGREGEACGTVGLLLEHSF  
EIDDSANFRKRGSLWNQDGTLSLSQRQLSEEERGRRLRDVAALNGLYRVRIIPRRPGALD  
GLEAGGYVSSFVPACSLVESHLSLQDLTLHVDVAGNVVGVSVVTHPGGCRGHEVEDVDLEL  
FNTSVQLQPPTTAPGPETAAFIERLEMEQAQKAKNPQEQKSFFAKYWMYIIPVVLFLMMS  
GAPDTGGQGGGGGGGGGGGSGLCCVPPSL

**Signal peptide:**  
amino acids 1-24

**Transmembrane domain:**  
amino acids 226-243

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**FIGURE 255**

GCGACGCGCGGCGGGGCGGCGAGAGGAAACGCGGCGCCGGGCGGGCCGGCCCTGGAGA  
TGGTCCCCGGCGCCGCGGGCTGGTGTGTCTCGTGCTCTGGCTCCCCGCGTGCGTCGCGG  
CCCACGGCTTCCGTATCCATGATTATTTGTACTTTCAAGTGCTGAGTCCTGGGGACATTC  
GATACATCTTCACAGCCACACCTGCCAAGGACTTTGGTGGTATCTTTCACACAAGGTATG  
AGCAGATTCACCTTGTCCCCGCTGAACCTCCAGAGGCCTGCGGGGAACCTCAGCAACGGTT  
TCTTCATCCAGGACCAGATTGCTCTGGTGGAGAGGGGGGGCTGCTCCTTCCTCTCCAAGA  
CTCGGGTGGTCCAGGAGCACGGCGGGCGGGCGGTGATCATCTCTGACAACGCAGTTGACA  
ATGACAGCTTCTACGTGGAGATGATCCAGGACAGTACCCAGCGCACAGCTGACATCCCCG  
CCCTCTTCCTGCTCGGCCGAGACGGCTACATGATCCGCCGCTCTCTGGAACAGCATGGGC  
TGCCATGGGCCATCATTTCCATCCCAGTCAATGTCACCAGCATCCCCACCTTTGAGCTGC  
TGCAACCGCCCTGGACCTTCTGGTTAGAAAGAGTTTGTCCCACATTCCAGCCATAAGTGA  
CTGAGCTGGGAAGGGGAAACCCAGGAATTTTGCTACTTGGAATTTGGAGATAGCATCTGG  
GGACAAGTGGAGCCAGGTAGAGGAAAAGGGTTTGGGCGTTGCTAGGCTGAAAGGGAAGCC  
ACACCACTGGCCTTCCCTTCCCCAGGGCCCCCAAGGGTGTCTCATGCTACAAGAAGAGGC  
AAGAGACAGGCCCCAGGGCTTCTGGCTAGAACCCGAAACAAAAGGAGCTGAAGGCAGGTG  
GCCTGAGAGCCATCTGTGACCTGTCACACTCACCTGGCTCCAGCCTCCCCTACCCAGGGT  
CTCTGCACAGTGACCTTCACAGCAGTTGTTGGAGTGGTTTAAAGAGCTGGTGTTTGGGGA  
CTCAATAAACCTCACTGACTTTTTAGCAATAAAGCTTCTCATCAGGGTTGCAAAAAAAA  
AAAAAAAAAAAAAAAAAAAA

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**FIGURE 256**

MVPGAAGWCCLVLWLPACVAAHGFRIDYLYFQVLSPGDIRYIFTATPAKDFGGIFHTRY  
EQIHLVPAEPPEACGELSNGFFIQDQIALVERGGCSFLSKTRVVQEHGGRAVIISDNAV  
NDSFYVEMIQDSTQRTADIPALFLLGRDGYMIRRSLEQHGLPWAIISIPVNVTSIPTFEL  
LQPPWTFW

**Signal peptide:**  
amino acids 1-20

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**FIGURE 257**

CTCGCTTCTTCCTTCTGGATGGGGGCCCAGGGGGCCCAGGAGAGTATAAAGGCGATGTGG  
AGGGTGCCCGGCACAACCAGACGCCCAGTCACAGGCGAGAGCCCTGGGATGCACCGGCCA  
GAGGCCATGCTGCTGCTGCTCACGCTTGCCCTCCTGGGGGGCCCCACCTGGGCAGGGAAG  
ATGTATGGCCCTGGAGGAGGCAAGTATTTTACGACCACTGAAGACTACGACCATGAAATC  
ACAGGGCTGCGGGTGTCTGTAGGTCTTCTCCTGGTGAAAAGTGTCAGGTGAAACTTGGA  
GACTCCTGGGACGTGAAACTGGGAGCCTTAGGTGGGAATACCCAGGAAGTCACCCTGCAG  
CCAGGCGAATACATCACAAAAGTCTTTGTGCGCTTCCAAGCTTTCCTCCGGGGTATGGTC  
ATGTACACCAGCAAGGACCGCTATTTCTATTTTGGGAAGCTTGATGGCCAGATCTCCTCT  
GCCTACCCCAGCCAAGAGGGGCAGGTGCTGGTGGGCATCTATGGCCAGTATCAACTCCTT  
GGCATCAAGAGCATTGGCTTTGAATGGAATTATCCACTAGAGGAGCCGACCACTGAGCCA  
CCAGTTAATCTCACATACTCAGCAAACCTACCCGTGGGTGCTAGGGTGGGGTATGGGGC  
CATCCGAGCTGAGGCCATCTGTGTGGTGGTGGCTGATGGTACTGGAGTAACTGAGTCGGG  
ACGCTGAATCTGAATCCACCAATAAATAAAGCTTCTGCAGAAA

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**FIGURE 258**

MHRPEAML<sup>1</sup>LL<sup>2</sup>LL<sup>3</sup>TL<sup>4</sup>ALL<sup>5</sup>GGPTWAGKMYGP<sup>6</sup>GGGKYFST<sup>7</sup>TEDYDHEITGLRVSVGL<sup>8</sup>LLVKS<sup>9</sup>VQ  
VKLGDSWDVKLGALGGNTQE<sup>10</sup>VTLPGEYITKV<sup>11</sup>FVAFQAFLRGMV<sup>12</sup>MYTSKDRYFYFGKLDG  
QISSAYPSQEGQVLVGIYGYQL<sup>13</sup>LGIKSIGFEWNYPLEEPTTEPPVNL<sup>14</sup>TYSANSPVGR

**Signal peptide:**  
amino acids 1-22

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**FIGURE 259**

CAGACATGGCTCAGTCACTGGCTCTGAGCCTCCTTATCCTGGTTCTGGCCTTTGGCATCC  
CCAGGACCCAAGGCAGTGATGGAGGGGCTCAGGACTGTTGCCTCAAGTACAGCCAAAGGA  
AGATTCCCGCCAAGGTTGTCCGCAGCTACCGGAAGCAGGAACCAAGCTTAGGCTGCTCCA  
TCCCAGCTATCCTGTTCTTGCCCCGCAAGCGCTCTCAGGCAGAGCTATGTGCAGACCCAA  
AGGAGCTCTGGGTGCAGCAGCTGATGCAGCATCTGGACAAGACACCATCCCCACAGAAAC  
CAGCCCAGGGCTGCAGGAAGGACAGGGGGGCCTCCAAGACTGGCAAGAAAGGAAAGGGCT  
CCAAAGGCTGCAAGAGGACTGAGCGGTCACAGACCCCTAAAGGGCCATAGCCCAGTGAGC  
AGCCTGGAGCCCTGGAGACCCACACAGCCTCACCAGCGCTTGAAGCCTGAACCCAAGATG  
CAAGAAGGAGGCTATGCTCAGGGGCCCTGGAGCAGCCACCCCATGCTGGCCTTGCCACAC  
TCTTTCTCCTGCTTTAACCACCCCATCTGCATTCCCAGCTCTACCCTGCATGGCTGAGCT  
GCCACAGCAGGCCAGGTCCAGAGAGACCGAGGAGGGAGAGTCTCCAGGGAGCATGAGA  
GGAGGCAGCAGGACTGTCCCCTTGAAGGAGAATCATCAGGACCCTGGACCTGATACGGCT  
CCCCAGTACACCCACCTCTTCCTTGTAATATGATTTATACCTAACTGAATAAAAAGCT  
GTTCTGTCTTCCCNCCCA

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**FIGURE 260**

MAQSLALSLLILVLAFGIPRTQGS DGG AQDCCLKYSQRKIPAKVVRSYRKQEPSLGCSIP  
AILFLPRKRSQAELCADPKELWVQQLMQHLDKTPSPQKPAQGCRKDRGASKTGKKKGKGSK  
GCKRTERSQTPKGP

**Important features of the protein:**

**Signal peptide:**

amino acids 1-17

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 67-71

**N-myristoylation sites:**

amino acids 17-23, 23-29, 27-33, 108-114, 118-124, 121-127

**Amidation site:**

amino acids 112-116

**Small cytokines:**

amino acids 51-91

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**FIGURE 261**

GGGACTACAAGCCGCGCCGCGCTGCCGCTGGCCCCCTCAGCAACCCTCGACATGGCGCTGA  
GGCGGCCACCGCGACTCCGGCTCTGCGCTCGGCTGCCTGACTTCTTCCTGCTGCTGCTTT  
TCAGGGGCTGCCTGATAGGGGCTGTAAATCTCAAATCCAGCAATCGAACCCAGTGGTAC  
AGGAATTTGAAAGTGTGGAAGTGTCTTGCATCATTACGGATTTCGAGACAAGTGACCCCA  
GGATCGAGTGGAAGAAAATTCAAGATGAACAAACCACATATGTGTTTTTTTGACAACAAAA  
TTCAGGGAGACTTGGCGGGTCGTGCAGAAATACTGGGGAAGACATCCCTGAAGATCTGGA  
ATGTGACACGGAGAGACTCAGCCCTTTATCGCTGTGAGGTCGTTGCTCGAAATGACCGCA  
AGGAAATTGATGAGATTGTGATCGAGTTAACTGTGCAAGTGAAGCCAGTGACCCCTGTCT  
GTAGAGTGCCGAAGGCTGTACCAGTAGGCAAGATGGCAACACTGCACTGCCAGGAGAGTG  
AGGGCCACCCCGGCCTCACTACAGCTGGTATCGCAATGATGTACCACTGCCACGGATT  
CCAGAGCCAATCCCAGATTTTCGAATTTCTTCTTTCCACTTAAACTCTGAAACAGGCACTT  
TGGTGTTCAGTGTCTGTTCAAGGACGACTCTGGGCAGTACTACTGCATTGCTTCCAATG  
ACGCAGGCTCAGCCAGGTGTGAGGAGCAGGAGATGGAAGTCTATGACCTGAACATTGGCG  
GAATTATTGGGGGGGTTCTGGTTGTCCTTGCTGTACTGGCCCTGATCACGTTGGGCATCT  
GCTGTGCATACAGACGTGGCTACTTCATCAACAATAAACAGGATGGAGAAAGTTACAAGA  
ACCCAGGGAAACCAGATGGAGTTAACTACATCCGCACTGACGAGGAGGGCGACTTCAGAC  
ACAAGTCATCGTTTTGTGATCTGAGACCCGCGGTGTGGCTGAGAGCGCACAGAGCGCACGT  
GCACATACCTCTGCTAGAAACTCCTGTCAAGGCAGCGAGAGCTGATGCACTCGGACAGAG  
CTAGACACTCATTGAGAAAGCTTTTCGTTTTGGCCAAAGTTGACCACTACTCTTCTTACTC  
TAACAAGCCACATGAATAGAAGAATTTTCCTCAAGATGGACCCGGTAAATATAACCACAA  
GGAAGCGAAACTGGGTGCGTTCACTGAGTTGGGTTCCCTAATCTGTTTTCTGGCCTGATTCC  
CGCATGAGTATTAGGGTGATCTTAAAGAGTTTGCTCACGTAAACGCCCGTGCTGGGCCCT  
GTGAAGCCAGCATGTTCACTACTGGTTCGTTGAGCAGCCACGACAGCACCATGTGAGATGG  
CGAGGTGGCTGGACAGCACCAGCAGCGCATCCCGGCGGGAACCCAGAAAAGGCTTCTTAC  
ACAGCAGCCTTACTTCATCGGCCACAGACACCACCGCAGTTTTCTTCTTAAAGGCTCTGC  
TGATCGGTGTTGCAGTGTCCATTGTGGAGAAGCTTTTTTGATCAGCATTGTTGTAATAACA  
ACCAAAATCAGGAAGGTAAATGGTTGCTGGAAGAGGGATCTTGCCTGAGGAACCTTGCT  
TGTCCAACAGGGTGTGAGGATTTAAGGAAAACCTTCGTCTTAGGCTAAGTCTGAAATGGT  
ACTGAAATATGCTTTTCTATGGGTCTTGTTTATTTTATAAAATTTTACATCTAAATTTTT  
GCTAAGGATGTATTTTGATTATTGAAAAGAAAATTTCTATTTAACTGTAAATATATTGT  
CATACAATGTAAATAACCTATTTTTTTTAAAAAAGTTCACTTAAGGTAGAAGTTCCAAG  
CTACTAGTGTAAATTTGAAAATATCAATAATTAAGAGTATTTTACCCAAGGAATCCTCT  
CATGGAAGTTTACTGTGATGTTCTTTTCTCACACAAGTTTTAGCCTTTTTTACAAGGGA  
ACTCATACTGTCTACACATCAGACCATAGTTGCTTAGGAAACCTTTAAAAATTTCCAGTTA  
AGCAATGTTGAAATCAGTTTGCATCTCTTCAAAAGAAACCTCTCAGGTTAGCTTTGAACT  
GCCTCTTCTGAGATGACTAGGACAGTCTGTACCCAGAGGCCACCCAGAAGCCCTCAGAT  
GTACATACACAGATGCCAGTCAGCTCCTGGGGTTGCGCCAGGCGCCCCCGCTCTAGCTCA  
CTGTTGCCTCGCTGTCTGCCAGGAGGCCCTGCCATCCTTGGGCCCCTGGCAGTGGCTGTGT  
CCCAGTGAGCTTTACTCACGTGGCCCTTGCTTCATCCAGCACAGCTCTCAGGTGGGCACT  
GCAGGGACACTGGTGTCTTCCATGTAGCGTCCCAGCTTTGGGCTCCTGTAACAGACCTCT  
TTTTGGTTATGGATGGCTCACAAAATAGGGCCCCCAATGCTATTTTTTTTTTTTAAAGTTT  
GTTTAATTATTTGTTAAGATTGTCTAAGGCCAAAGGCAATTGCGAAATCAAGTCTGTCAA  
GTACAATAACATTTTTTAAAAGAAAATGGATCCCACTGTTTCTTGGCCACAGAGAAAGC  
ACCCAGACGCCACAGGCTCTGTGCGATTTCAAAACAAACCATGATGGAGTGGCGGCCAGT  
CCAGCCTTTTAAAGAACGTGAGGTGGAGCAGCCAGGTGAAAGGCCTGGCGGGGAGGAAAG  
TGAAACGCCTGAATCAAAAGCAGTTTTCTAATTTTGACTTTAAATTTTTTATCCGCCGGA



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GACACTGCTCCCATTTGTGGGGGGACATTAGCAACATCACTCAGAAGCCTGTGTTCTTCA  
AGAGCAGGTGTTCTCAGCCTCACATGCCCTGCCGTGCTGGACTCAGGACTGAAGTGCTGT  
AAAGCAAGGAGCTGCTGAGAAGGAGCACTCCACTGTGTGCCTGGAGAATGGCTCTCACTA  
CTCACCTTGTCTTTCAGCTTCCAGTGTCTTGGGTTTTTTTATACTTTGACAGCTTTTTTTT  
AATTGCATACATGAGACTGTGTTGACTTTTTTTTAGTTATGTGAAACACTTTGCCGCAGGC  
CGCCTGGCAGAGGCAGGAAATGCTCCAGCAGTGGCTCAGTGCTCCCTGGTGTCTGCTGCA  
TGGCATCCTGGATGCTTAGCATGCAAGTTCCCTCCATCATTGCCACCTTGGTAGAGAGGG  
ATGGCTCCCCACCTCAGCGTTGGGGATTACAGCTCCAGCCTCCTTCTTGGTTGTCATAG  
TGATAGGGTAGCCTTATTGCCCCCTCTTCTTATACCCTAAAACCTTCTACACTAGTGCCA  
TGGGAACCAGGTCTGAAAAAGTAGAGAGAAGTGAAAGTAGAGTCTGGGAAGTAGCTGCCT  
ATAACTGAGACTAGACGGAAAAGGAATACTCGTGTATTTTAAGATATGAATGTGACTCAA  
GACTCGAGGCCGATACGAGGCTGTGATTCTGCCTTTGGATGGATGTTGCTGTACACAGAT  
GCTACAGACTTGTACTAACACACCGTAATTTGGCATTGTGTTAACCTCATTTATAAAAGC  
TTCAAAAAAACCCA

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**FIGURE 262**

MALRRPPRLRLCARLPDFFLLLLFRGCLIGAVNLKSSNRTPVVQEFESVELSCIITDSQT  
SDPRIEWKKIQDEQTTYVFFDNKIQGDLGRAEILGKTSLSKIWNVTRRDSALYRCEVVAR  
·NDRKEIDEIVIELTVQVKPVTVPVCRVPKAVPVGKMATLHCQSEGHPRPHYSWYRNDVPL  
PTDSRANPRFRNSSFHLNSETGTLVFTAVHKDDSGQYYCIASNDAGSARCEEQEMEVDL  
NIGGIIGGVLVVLAVLALITLGICCAYYRRGYFINNKQDGESYKNPGKPDGVNYIRTDEEG  
DFRHKSSFVI

**Important features of the protein:****Signal peptide:**

amino acids 1-30

**Transmembrane domain:**

amino acids 243-263

**N-glycosylation sites:**

amino acids 104-107, 192-195

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 107-110

**Casein kinase II phosphorylation site:**

amino acids 106-109, 296-299

**Tyrosine kinase phosphorylation site:**

amino acids 69-77

**N-myristoylation sites:**

amino acids 26-31, 215-220, 226-231, 243-248, 244-249, 262-267

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**FIGURE 263**

CCAGGACCAGGGCGCACCCGGCTCAGCCTCTCACTTGTCTCAGAGGCCGGGGAAGAGAAGCAA  
AGCGCAACGGTGTGGTCCAAGCCGGGGCTTCTGCTTCGCCTCTAGGACATACACGGGACC  
CCCTAACTTCAGTCCCCCAAACGCGCACCCCTCGAAGTCTTGAAGTCCAGCCCCGCACATC  
CACGCGCGGCACAGGCGCGGCAGGCGGCAGGTCCCGGCCGAAGGCGATGCGCGCAGGGGG  
TCGGGCAGCTGGGCTCGGGCGGGCGGGAGTAGGGCCCCGGCAGGGAGGCAGGGAGGCTGCAT  
ATTCAGAGTCGCGGGCTGCGCCCTGGGCAGAGGCCGCCCTCGCTCCACGCAACACCTGCT  
GCTGCCACCGCGCCGCGATGAGCCGCGTGGTCTCGCTGCTGCTGGGCGCCGCGCTGCTCT  
GCGGCCACGGAGCCTTCTGCCGCCGCGTGGTCTCAGCGGCCAAAAGGTGTGTTTTGCTGACT  
TCAAGCATCCCTGCTACAAAATGGCCTACTTCCATGAACTGTCCAGCCGAGTGAGCTTTC  
AGGAGGCACGCTGGCTTGTGAGAGTGAGGGAGGAGTCCTCCTCAGCCTTGAGAATGAAG  
CAGAACAGAAGTTAATAGAGAGCATGTTGCAAAACCTGACAAAACCCGGGACAGGGATTT  
CTGATGGTGATTTCTGGATAGGGCTTTGGAGGAATGGAGATGGGGCAAACATCTGGTGCCT  
GCCCAGATCTCTACCAGTGGTCTGATGGAAGCAATTCCCAGTACCGAAACTGGTACACAG  
ATGAACCTTCCCTGCGGAAGTGAAAAGTGTGTTGTGATGTATCACCAACCAACTGCCAATC  
CTGGCCTTGGGGGTCCCTACCTTTACCAGTGGAAATGATGACAGGTGTAACATGAAGCACA  
ATTATATTTGCAAGTATGAACCAGAGATTAATCCAACAGCCCCCTGTAGAAAAGCCTTATC  
TTACAAATCAACCAGGAGACACCCATCAGAATGTGGTTGTTACTGAAGCAGGTATAATTC  
CCAATCTAATTTATGTTGTTATACCAACAATACCCCTGCTCTTACTGATACTGGTTGCTT  
TTGGAACCTGTTGTTTCCAGATGCTGCATAAAAGTAAAGGAAGAACAAAACTAGTCCAA  
ACCAGTCTACACTGTGGATTTCAAAGAGTACCAGAAAAGAAAGTGGCATGGAAGTATAAAT  
AACTCATTGACTTGGTTCCAGAATTTTGTAAATCTGGATCTGTATAAGGAATGGCATCAG  
ACAATAGCTTGGAAATGGCTTGAAATCACAAAGGATCTGCAAGATGAACTGTAAGCTCCC  
CCTTGAGGCAAATATTAAGTAATTTTATATGTCTATTATTTCATTTAAAGAATATGCT  
GTGCTAATAATGGAGTGAGACATGCTTATTTTGCTAAAGGATGCACCCAACTTCAAAC  
TCAAGCAAATGAAATGGACAATGCAGATAAAGTTGTTATCAACACGTGGGAGTATGTGT  
GTTAGAAGCAATTCCTTTTATTTCTTTCACCTTTCATAAGTTGTTATCTAGTCAATGTAA  
TGATATATTGTATTGAAATTTACAGTGTGCAAAAGTATTTTACCTTTGCATAAGTGTTTGA  
TAAAAATGAACTGTTCTAATATTTATTTTTATGGCATCTCATTTTTCAATACATGCTCTT  
TTGATTAAAGAACTTATTACTGTTGTCAACTGAATTCACACACACACAAATATAGTACC  
ATAGAAAAAGTTTGTCTTCGAAATAATTATCTTTTCTGCTTTTGGTCAAT  
GTCTAGGAAATCTCTTCAGAAATAAGAAGCTATTTTCAATTAAGTGTGATATAAACCTCCTC  
AAACATTTTACTTAGAGGCAAGGATTGTCTAATTTCAATTGTGCAAGACATGTGCCTTAT  
AATTATTTTACTTAAATTTAAACAGATTTTGTAAATAATGTAACCTTTGTTAATAGGTGC  
ATAAACACTAATGCAGTCAATTTGAACAAAAGAAGTGACATACACAATATAAATCATATG  
TCTTCACACGTTGCCTATATAATGAGAAGCAGCTCTCTGAGGGTTCTGAAATCAATGTGG  
TCCCTCTCTTGCCCACTAAACAAAGATGGTTGTTTCGGGGTTTGGGATTGACACTGGAGGC  
AGATAGTTGCAAAGTTAGTCTAAGGTTTCCCTAGCTGTATTTAGCCTCTGACTATATTAG  
TATACAAAGAGGTCATGTGGTTGAGACCAGGTGAATAGTCACTATCAGTGTGGAGACAAG  
CACAGCACACAGACATTTTAGGAAGGAAAGGAACACGAAATCGTGTGAAAATGGGTGG  
AACCCATCAGTGATCGCATATTCATTGATGAGGGTTTGGCTTGAGATAGAAAATGGTGGCT  
CCTTCTGTCTTATCTCCTAGTTTCTTCAATGCTTACGCCTTGTTCTTCTCAAGAGAAAG  
TTGTAACCTCTCTGGTCTTCATATGTCCCTGTGCTCCTTTTAAACCAATAAAGAGTTCTTG  
TTTCTGGGGGAAA

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**FIGURE 264**

MSRVVSLLLGAALLCGHGAFRRVVSQKVCFAFKHPCYKMAFHELSRVSFQEARLA  
CESEGGVLLSLENEAEQKLIESMLQNLTKPGTGISDGDFWIGLWRNGDGQTSACPDLYQ  
WSDGSNSQYRNWYTDEPSCGSEKCVVMYHQPTANPGLGGPYLYQWNDDRCNMKHNKY  
EPEINPTAPVEKPYLTNQP GDTHQNVVTEAGIIPNLIYVVIPTIPLLLLILVAFGTCCF  
QMLHKSKGRTKTSPNQSTLWISKSTRKESGMEV

**Important features of the protein:****Signal peptide:**

amino acids 1-21

**Transmembrane domain:**

amino acids 214-235

**N-glycosylation sites:**

amino acids 86-89 and 255-258

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 266-269

**N-myristoylation sites:**

amino acids 27-32, 66-71, 91-96, 93-98, 102-107, 109-114, 140-145 and 212-217

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**FIGURE 265**

GGAGAATGGAGAGAGCAGTGAGAGTGGAGTCCGGGGTCCTGGTCGGGGTGGTCTGTCTGC  
TCCTGGCATGCCCTGCCACAGCCACTGGGCCCCGAAGTTGCTCAGCCTGAAGTAGACACCA  
CCCTGGGTCGTGTGCGAGGCCGGCAGGTGGGCGTGAAGGGCACAGACCGCCTTGTGAATG  
TCTTTCTGGGCATTCCATTGCCCAGCCGCCACTGGGCCCTGACCGGTTCTCAGCCCCAC  
ACCCAGCACAGCCCTGGGAGGGTGTGCGGGATGCCAGCACTGCGCCCCAATGTGCCTAC  
AAGACGTGGAGAGCATGAACAGCAGCAGATTTGTCCTCAACGGAAAACAGCAGATCTTCT  
CCGTTTCAGAGGACTGCCTGGTCCTCAACGTCTATAGCCCAGCTGAGGTCCCCGAGGGT  
CCGGTAGGCCGGTCATGGTATGGGTCCATGGAGGCGCTCTGATAACTGGCGCTGCCACCT  
CCTACGATGGATCAGCTCTGGCTGCCTATGGGGATGTGGTTCGTGGTTACAGTCCAGTACC  
GCCTTGGGGTCCTTGGCTTCTTCAGCACTGGAGATGAGCATGCACCTGGCAACCAGGGCT  
TCCTAGATGTGGTAGCTGCTTTGCGCTGGGTGCAAGAAAACATCGCCCCCTTCGGGGGTG  
ACCTCAACTGTGTCACTGTCTTTGGTGGATCTGCCGGTGGGAGCATCATCTCTGGCCTGG  
TCCTGTCCCCAGTGGCTGCAGGGCTGTTCCACAGAGCCATCACACAGAGTGGGGTCATCA  
CCACCCCAGGGATCATCGACTCTCACCCCTGGCCCCTAGCTCAGAAAATCGAAACACCT  
TGGCCTGCAGCTCCAGCTCCCCGGCTGAGATGGTGCAGTGCCTTCAGCAGAAAGAAGGAG  
AAGAGCTGGTCCTTAGCAAGAAGCTGAAAAATACTATCTATCCTCTCACCGTTGATGGCA  
CTGTCTTCCCCAAAAGCCCCAAGGAACCTCCTGAAGGAGAAGCCCTTCCACTCTGTGCCCT  
TCCTCATGGGTGTCAACAACCATGAGTTCAGCTGGCTCATCCCCAGGGGCTGGGGTCTCC  
TGGATACAATGGAGCAGATGAGCCGGGAGGACATGCTGGCCATCTCAACACCCGTCTTGA  
CCAGTCTGGATGTGCCCCCTGAGATGATGCCACCGTCATAGATGAATACCTAGGAAGCA  
ACTCGGACGCACAAGCCAAATGCCAGGCGTTCCAGGAATTTCATGGGTGACGTATTTCATCA  
ATGTTCCACCGTCAGTTTTTCAAGATACCTTCGAGATTCTGGAAGCCCTGTCTTTTTCT  
ATGAGTTCAGCATCGACCCAGTTCCTTTTGCAGAGATCAAACCTGCCTGGGTGAAGGCTG  
ATCATGGGGCCGAGGGTGCTTTTTGTGTTCCGAGGTCCCTTCCTCATGGACGAGAGCTCCC  
GCCTGGCCTTTCCAGAGGCCACAGAGGAGGAGAAGCAGCTAAGCCTCACCATGATGGCCC  
AGTGGACCCACTTTGCCCCGACAGGGGACCCCAATAGCAAGGCTCTGCCTCCTTGGCCCC  
AATTCAACCAGGCGGAACAATATCTGGAGATCAACCCAGTGCCACGGGCCGGACAGAAGT  
TCAGGGAGGCCTGGATGCAGTTCCTGGTCAGAGACGCTCCCCAGCAAGATAACAAGTGGC  
ACCAGAAGCAGAAGAACAGGAAGGCCAGGAGGACCTCTGAGAGGCCAGGCCTGAACCTTCT  
TGGCTGGGGCAAACCACTCTTCAAGTGGTGGCAGAGTCCCAGCACGGCAGCCCGCCTCTC  
CCCCTGCTGAGACTTTAATCTCCACCAGCCCTTAAAGTGTGCGCCGCTCTGTGACTGGAG  
TTATGCTCTTTTGAATGTCAAGGCCGCTCCACCTCTGGGGCATTGTACAAGTTCT  
TCCCTCTCCCTGAAGTGCTTTCTCTGCTTTCTTCGTGGTAGGTTCTAGCACATTCTCTA  
GCTTCCTGGAGGACTCACTCCCCAGGAAGCCTTCCCTGCCTTCTCTGGGCTGTGCGGCCC  
CGAGTCTGCGTCCATTAGAGCACAGTCCACCCGAGGCTAGCACCGTGTCTGTGTCTGTCT  
CCCCCTCAGAGGAGCTCTCTCAAAATGGGGATTAGCCTAACCCCACTCTGTCACCACAC  
CAGGATCGGGTGGGACCTGGAGCTAGGGGGTGTGTTGCTGAGTGAGTGAGTGAAACACAGA  
ATATGGGAATGGCAGCTGCTGAACCTGAACCCAGAGCCTTCAGGTGCCAAAGCCATACTC  
AGGCCCCCACCACATTGTCCACCCTGGCCAGAAGGGTGCATGCCAATGGCAGAGACCTG  
GGATGGGAGAAGTCTGGGGCGCCAGGGGATCCAGCCTAGAGCAGACCTTAGCCCCCTGAC  
TAAGGCCTCAGACTAGGGCGGGAGGGGTCTCCTCCTCTCTGCTGCCAGTCTGGCCCCCT  
GCACAAGACAACAGAATCCATCAGGGCCATGAGTGTACCCAGACCTGACCTCACCAAT  
TCCAGCCCCCTGACCTCAGGACGCTGGATGCCAGCTCCCAGCCCCAGTGCCGGGTCTCTCC  
CTCCCTTCTCTGGCTTGGGGAGACCAGTTTCTGGGGAGCTTCCAAGAGCACCCACCAAGAC  
ACAGCAGGACAGGCCAGGGGAGGGCATCTGGACCAGGGCATCCGTGGGGCTATTGTACA  
GAGAAAAGAAGAGACCCACCACTCGGGCTGCAAAAGGTGAAAAGCACCAAGAGGTTTTTC

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AGATGGAAGTGAGAGGTGACAGTGTGCTGGCAGCCCTCACAGCCCTCGCTTGCTCTCCCT  
GCCGCCTCTGCCTGGGCTCCCACTTTGGCAGCACTTGAGGAGCCCTTCAACCCGCCGCTG  
CACTGTAGGAGCCCCCTTTCTGGGCTGGCCAAGGCCGGAGCCAGCTCCCTCAGCTTGCGGG  
GAGGTGCGGAGGGAGAGGGGCGGGCAGGAACCGGGGCTGCGCGCAGCGCTTGCGGGCCAG  
AGTGAGTTCGGGTGGGCGTGGGCTCGGCGGGGCCCCACTCAGAGCAGCTGGCCGGCCCC  
AGGCAGTGAGGGCCTTAGCACCTGGGCCAGCAGCTGCTGTGCTCGATTTCTCGCTGGGCC  
TTAGCTGCCTCCCCGCGGGGCAGGGCTCGGGACCTGCAGCCCTCCATGCCTGACCCTCCC  
CCCACCCCCCGTGGGCTCCTGTGCGGCCGGAGCCTCCCCAAGGAGCGCCGCCCCCTGCTC  
CACAGCGCCCAAGTCCCATCGACCACCCAAGGGCTGAGGAGTGCGGGTGACAGCGCGGGA  
CTGGCAGGCAGCTCCACCTGCTGCCCCAGTGCTGGATCCACTGGGTGAAGCCAGCTGGGC  
TCCTGAGTCTGGTGGGGACTTGGAGAACCCTTTATGTCTAGCTAAGGGATTGTAAATACAC  
CGATGGGCACTCTGTATCTAGCTCAAGGTTTGTAAACACACCAATCAGCACCCCTGTGTCT  
AGCTCAGTGTTTGTGAATGCACCAATCCACACTCTGTATCTGGCTACTCTGGTGGGGACT  
TGGAGAACCTTTGTGTCCACACTCTGTATCTAGCTAATCTAGTGGGGATGTGGAGAACCT  
TTGTGTCTAGCTCAGGGATCGTAAACGCACCAATCAGCACCCCTGTCAAAACAGACCACTT  
GACTCTCTGTAAATGGACCAATCAGCAGGATGTGGGTGGGGCGAGACAAGAGAATAAAA  
GCAGGCTGCCTGAGCCAGCAGTGACAACCCCCCTCGGGTCCCCTCCACGCCGTGGAAGC  
TTTGTTCCTTCGCTCTTTGCAATAAATCTTGCTACTGCCCAAAA

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**FIGURE 266**

MERAVRVESGVLVGVVCLLLACPATATGPEVAQPEVDTTLGRVRGRQVGVKGTDRLVNVF  
LGIPFAQPPLGPD RFSAPHPAQPWEGVRDASTAPPMCLQDVESMNSSRFVLNGKQQIFSV  
SEDCLVLNVYSPA EVPAGSGRPVMVWVHGGALITGAATSYDGSALAAYGDVVVVTVQYRL  
GVLGFFSTGDEHAPGNQGF LDVVAALRWVQENIAPFGDLN CVTVFGGSAGGSIISGLVL  
SPVAAGLFHRAITQSGVITTPGIIDSHPWPLAQKIAN TLACSSSSPAEMVQCLQQKEGEE  
LVL SKKLKNTIYPLTVDGTVPKSPKELLKEKPFHSVPFLMGVNNHEFSWLI PRGWGLLD  
TMEQMSREDMLAISTPVLTS LDVPPPEMMPTVIDEYLG SNSDAQAKCQAFQEFMGDVFINV  
PTVSFSRYLRDSGSPVFFYEFQHRPSSF AKIKPAWVKADHGAEGAFVFGGPFLMDESSL  
AFPEATEEEKQLSLTMMAQWTHFARTGDPNSKALPPWPQFNQAEQYLEINPVPRAGQKFR  
EAWMQFWSETLPSKIQQWHQKQKNRKAQEDL

**Important features of the protein:**

**Signal peptide:**

amino acids 1-27

**Transmembrane domain:**

amino acids 226-245

**N-glycosylation site:**

amino acids 105-109

**N-myristoylation sites:**

amino acids 10-16, 49-55, 62-68, 86-92, 150-156, 155-161,  
162-168, 217-223, 227-233, 228-234, 232-238, 262-268, 357-363,  
461-467

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 12-23

**Carboxylesterases type-B serine active site:**

amino acids 216-232

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**FIGURE 267**

TGTCGCCTGGCCCTCGCCATGCAGACCCCGCGAGCGTCCCCTCCCCGCCCCGGCCCTCCTG  
CTTCTGCTGCTGCTACTGGGGGGCGCCACGGCCTCTTTCCTGAGGAGCCGCCGCCGCTT  
AGCGTGGCCCCCAGGGACTACCTGAACCACTATCCCGTGTTTGTGGGCAGCGGGCCCCGGA  
CGCCTGACCCCCCGCAGAAGGTGCTGACGACCTCAACATCCAGCGAGTCCTGCGGGTCAAC  
AGGACGCTGTTCAATTGGGGACAGGGACAACCTCTACCGCGTAGAGCTGGAGCCCCCCACG  
TCCACGGAGCTGCGGTACCAGAGGAAGCTGACCTGGAGATCTAACCCCAGCGACATAAAC  
GTGTGTTCGGATGAAGGGCAAACAGGAGGGCGAGTGTCGAAACTTCGTAAAGGTGCTGCTC  
CTTCGGGACGAGTCCACGCTCTTTGTGTGCGGTTCCAACGCCTTCAACCCGGTGTGCGCC  
AACTACAGCATAGACACCCTGCAGCCCGTCGGAGACAACATCAGCGGTATGGCCCCGCTGC  
CCGTACGACCCCAAGCACGCCAATGTTGCCCTCTTCTCTGACGGGATGCTCTTACAGCT  
ACTGTTACCGACTTCTAGCCATTGATGCTGTCTATCTACCGCAGCCTCGGGGACAGGCCC  
ACCTTGCGCACCGTGAAACATGACTCCAAGTGTTCAAAGAGCCTTACTTTGTCCATGCG  
GTGGAGTGGGGCAGCCATGTCTACTTCTTCTTCCGGGAGATTGCGATGGAGTTTAACTAC  
CTGGAGAAGGTGGTGGTGTCCCGCGTGGCCCCGAGTGTCGCAAGAACGACGTGGGAGGCTCC  
CCCCGCGTGCTGGAGAAGCAGTGGACGTCCTTCTGAAGGCGCGGCTCAACTGCTCTGTA  
CCCGGAGACTCCCATTTCTACTTCAACGTGCTGCAGGCTGTACGGGCGTGCTGAGCCTC  
GGGGGCCGGCCCGTGCTGCTGCGCGTTTTTTCCACGCCCAGCAACAGCATCCCTGGCTCG  
GCTGTCTGCGCCTTTGACCTGACACAGGTGGCAGCTGTGTTTGAAGGCCGCTTCCGAGAG  
CAGAAGTCCCCCGAGTCCATCTGGACGCCGGTGCCGGAGGATCAGGTGCCTCGACCCCGG  
CCCGGGTGCTGCGCAGCCCCCGGGATGCAGTACAATGCCTCCAGCGCCTTGCCGGATGAC  
ATCCTCAACTTTGTCAAGACCCACCTCTGATGGACGAGGCGGTGCCCTCGCTGGGCCAT  
GCGCCCTGGATCCTGCGGACCCTGATGAGGCACCAGCTGACTCGAGTGGCTGTGGACGTG  
GGAGCCGGCCCCCTGGGGCAACCAGACCGTTGTCTTCTGGGTTCTGAGGCGGGGACGGTC  
CTCAAGTTCTCGTCCGGCCCAATGCCAGCACCTCAGGGACGTCTGGGCTCAGTGTCTTC  
CTGGAGGAGTTTGAGACCTACCGGCCGGACAGGTGTGGACGGCCCCGGCGGTGGCGAGACA  
GGGCAGCGGCTGCTGAGCTTGAGCTGGACGCAGCTTCCGGGGGGCCTGCTGGCTGCCTTC  
CCCCGCTGCGTGCTCCGAGTGCCTGTGGCTCGCTGCCAGCAGTACTCGGGGTGTATGAAG  
AACTGTATCGGCAGTCAGGACCCCTACTGCGGGTGGGCCCCCGACGGCTCCTGCATCTTC  
CTCAGCCCCGGGCACCAGAGCCGCCTTTGAGCAGGACGTGTCCGGGGCCAGCACCTCAGGC  
TTAGGGGACTGCACAGGACTCCTGCGGGCCAGCCTCTCCGAGGACCGCGCGGGGCTGGTG  
TCGGTGAACCTGCTGGTAACGTCGTCGGTGGCGGCCCTTCGTGGTGGGAGCCGTGGTGTCC  
GGCTTCAGCGTGGGCTGGTTTCGTGGGCCTCCGTGAGCGGCGGGAGCTGGCCCCGGCGCAAG  
GACAAGGAGGCCATCCTGGCGCACGGGGCGGGCGAGGCGGTGCTGAGCGTCAGCCGCCTG  
GGCGAGCGCAGGGCGCAGGGTCCCGGGGGCGGGGCGGAGGCGGTGGCGGTGGCGCCGGG  
GTTCCCCCGGAGGCCCTGCTGGCGCCCCCTGATGCAGAACGGCTGGGCCAAGGCCACGCTG  
CTGCAGGGCGGGCCCCACGACCTGGACTCGGGGCTGCTGCCACGCCCCGAGCAGACGCCG  
CTGCCGCGAGAAGCGCCTGCCCACTCCGCACCCGCACCCCCACGCCCTGGGCCCCCCGCGCC  
TGGGACCACGGCCACCCCCCTGCTCCCGGCCTCCGCTTCACTCTCCTCCTGCTGCTGGCG  
CCCGCCCCGGGCCCCCGAGCAGCCCCCGCGCCTGGGGAGCCGACCCCCGACGGCCGCCTC  
TATGCTGCCCCGGCCCGGCCGCGCCTCCACGGCGACTTCCCGCTACCCCCACGCCAGC  
CCGGACCGCCGGCGGGTGGTGTCCGCGCCACGGGCCCCCTTGACCCAGCCTCAGCCGCC  
GATGGCCTCCCGCGGCCCTGGAGCCCGCCCCGACGGGCAGCCTGAGGAGGCCACTGGGC  
CCCCACGCCCCCTCCGGCCGCCACCTGCGCCGCACCCACACGTTCAACAGCGGCGAGGCC  
CGGCCTGGGGACCGCCACCGCGGCTGCCACGCCCCGGCGGGCACAGACTTGGCCACCTC  
CTCCCCATATGGGGGGCGGACAGGACTGCGCCCCCGTGCCCTAGGCCGGGGGCCCCCG  
ATGCCTTGGCAGTGCCAGCCACGGGAACCAGGAGCGAGAGACGGTGCCAGAACGCCGGGG  
CCCGGGGCAACTCCGAGTGGGTGCTCAAGTCCCCCCCCGCGACCCACCCGCGGAGTGGGGG



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GCCCCCTCCGCCACAAGGAAGCACAACCAGCTCGCCCTCCCCCTACCCGGGGCCGCAGGA  
CGCTGAGACGGTTTTGGGGGTGGGTGGGCGGGAGGACTTTGCTATGGATTTGAGGTTGACC  
TTATGCGCGTAGGTTTTGGTTTTTTTTTGCAGTTTTGGTTTCTTTTGCGGTTTTCTAACC  
AATTGCACAACCTCCGTTCTCGGGGTGGCGGCAGGCAGGGGAGGCTTGGACGCCGGTGGGG  
AATGGGGGGCCACAGCTGCAGACCTAAGCCCTCCCCACCCCTGGAAAGGTCCCTCCCCA  
ACCCAGGCCCCCTGGCGTGTGTGGGTGTGCGTGCGTGTGCGTGCCGTGTTCTGTGTGCAAGG  
GGCCGGGGAGGTGGGCGTGTGTGTGCGTGCCAGCGAAGGCTGCTGTGGGCGTGTGTGTCA  
AGTGGGCCACGCGTGCAGGTTGTGTGTCCACGAGCGACGATCGTGGTGGCCCCAGCGGCC  
TGGGCGTTGGCTGAGCCGACGCTGGGGCTTCCAGAAGGCCCGGGGTCTCCGAGGTGCCG  
GTTAGGAGTTTGAACCCCCCCCCACTCTGCAGAGGGAAGCGGGGACAATGCCGGGGTTTCA  
GGCAGGAGACACGAGGAGGGCCTGCCCCGAAGTCACATCGGCAGCAGCTGTCTAAAGGGC  
TTGGGGGCCTGGGGGGCGGCGAAGGTGGGTGGGGCCCCCTCTGTAAATACGGCCCCAGGGT  
GGTGAGAGAGTCCCATGCCACCCGTCCCCTTGTGACCTCCCCCTATGACCTCCAGCTGA  
CCATGCATGCCACGTGGCTGGCTGGGTCCCTCTGCCCTCTTTGGAGTTTGCTCCCCCAGC  
CCCCTCCCCATCAATAAAACTCTGTTTACAACCAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 268**

MQTPRASPPRPALLLLLLLLLLLGGAHGLFPEEPPPLSVAPRDYLNHYVPFVVGSGPGRLTPAE  
GADDLNIQRLRVLRVNRTLFIGDRDNLRYVELEPPTSTELRYQRKLTWRSNPSDINVCRMKG  
KQEGECRNFKVLLLRDESTLFVCGSNAFNPVCANYSIDTLQPVGDNISGMARCPYDPKH  
ANVALFSDGMLFTATVTDFLAIDAVIYRSLGDRPTLRTVKHDSKWFKEPYFVHAVEWGSH  
VYFFFREIAMEFNYLEKVVVSRVARVCKNDVGGSPRVLEKQWTSFLKARLNCSPVGD SHF  
YFNVLQAVTGVS LGGRPVLAVFSTPSNSIPGSAVCAFDLTQVA AVFEGRFREQKSPES  
IWTPVPEDQVPRPRPGCCAAPGMQYNASSALPDDILNFVKTHPLMDEAVPSLG HAPWILR  
TLMRHQLTRVAVDVGAGPWGNQTVVFLGSEAGTVLKFLVRPNASTSGTSGLSVFLEEFET  
YRPDRCGRPGGGETGQRLLSLELDAASGGLLA AFPRCVVRVPVARCQQYSGCMKNCIGSQ  
DPYCGWAPDGSCIFLSPGTRAAFEQDVSGASTSGLGDCTGLLRASLSEDRAGLVSVNLLV  
TSSVAAFVVGAVVSGFSVGWFVGLRERRELARRKDKEAILAHGAGEAVLSVSRLGERRAQ  
GPGGRGGGGGGGAGVPPEALLAPLMQNGWAKATLLQGGPHDLDSGLLPTPEQTPLPQKRL  
PTPHPHPHALGPRAWDHGHPLLPASASSSLLLLAPARAPEQPPAPGEPTPDGRLYAARPG  
RASHGDFPLTPHASPD RRRVVSAPTGPLDPASAADGLPRPWSPPTGSLRRPLGPHAPPA  
ATLRRTHTFNSGEARPGDRHRGCHARPGTDLAHL LPYGGADRTAPPVP

**Important features of the protein:****Signal peptide:**

amino acids 1-25

**Transmembrane domains:**

amino acids 318-339, 598-617

**N-glycosylation sites.**amino acids 74-78, 155-159, 167-171, 291-295, 386-390,  
441-445, 462-466**Glycosaminoglycan attachment sites:**

amino acids 51-55, 573-577

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 102-106

**N-myristoylation sites:**amino acids 21-27, 50-56, 189-195, 333-339, 382-388, 448-454,  
490-496, 491-497, 508-514, 509-515, 531-537, 558-564, 569-575,  
574-580, 580-586, 610-616, 643-649, 663-669, 666-672, 667-673,  
668-674, 669-675, 670-676, 868-874, 879-885

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**FIGURE 269**

ATCTGAGTGAGCTAACTGACACAATGAAACTGTCAGGCATGTTTCTGCTCCTCTCTCTGG  
CTCTTTTCTGCTTTTAAACAGGTGTCTTCAGTCAGGGAGGACAGGTTGACTGTGGTGAGT  
TCCAGGACCCCAAGGTCTACTGCACTCGGGAATCTAACCACACTGTGGCTCTGATGGCC  
AGACATATGGCAATAAATGTGCCTTCTGTAAGGCCATAGTGAAAAGTGGTGGAAAGATTA  
GCCTAAAGCATCCTGGAAAATGCTGAGTTAAAGCCAATGTTTCTTGGTGACTTGCCAGCT  
TTTGCAGCCTTCTTTTCTCACTTCTGCTTATACTTTTGCTGGTGGATTCTTTAATTCAT  
AAAGACATACCTACTCTGCCTGGGTCTTGAGGAGTTCAATGTATGTCTATTTCTCTTGAT  
TCACTTGTCATAAAGTACATTCTGCAAAAGCAAAA

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## FIGURE 270

MKLSGMFLLLSLALFCFLTGVFSQGGQVDCGEFQDPKVYCTRESNPFCGSDGQTYGNKCA  
FCKAIVKSGGKISLKHPGKC

**Important features of the protein:**

**Signal peptide:**

amino acids 1-23

**N-myristoylation sites:**

amino acids 26-32, 52-58, 56-62, 69-75

**Kazal serine protease inhibitors family signature:**

amino acids 40-63

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**FIGURE 271**

AACTTCTACATGGGCCTCCTGCTGCTGGTGCTCTTCCTCAGCCTCCTGCCGGTGGCCTAC  
ACCATCATGTCCCTCCCACCCTCCTTTGACTGCGGGCCGTTCAGGTGCAGAGTCTCAGTT  
GCCCCGGGAGCACCTCCCCTCCCGAGGCAGTCTGCTCAGAGGGCCTCGGCCCAGAATTCCA  
GTTCTGGTTTTCATGCCAGCCTGTAAAAGGCCATGGAACTTTGGGTGAATCACCGATGCCA  
TTTAAGAGGGTTTTCTGCCAGGATGGAAATGTTAGGTCGTTCTGTGTCTGCGCTGTTTCAT  
TTCAGTAGCCACCAGCCACCTGTGGCCGTTGAGTGCTTGAAATGAGGAACTGAGAAAATT  
AATTTCTCATGTATTTTTTCTCATTTATTTATTAATTTTTTAACTGATAGTTGTACATATTT  
GGGGGTACATGTGATATTTGGATACATGTATACAATATATAATGATCAAATCAGGGTAAC  
TGGGATATCCATCACATCAAACATTTATTTTTTTATTCTTTTTTAGACAGAGTCTCACTCTG  
TCACCCAGGCTGGAGTGCAGTGGTGCCATCTCAGCTTACTGCAACCTCTGCCTGCCAGGT  
TCAAGCGATTCTCATGCCTCCACCTCCCAAGTAGCTGGGACTACAGGCATGCACCACAAT  
GCCCCAACTAATTTTTGTATTTTTTAGTAGAGACGGGGTTTTGCCATGTTGCCAGGCTGGC  
CTTGAACCTCTGGCCTCAAACAATCCACTTGCCTCGGCCTCCCAAGTGTTATGATTACA  
GGCGTGAGCCACCGTGCCTGGCCTAAACATTTATCTTTTCTTTGTGTTGGGAACTTTGAA  
ATTATACAATGAATTATTGTTAACTGTCATCTCCCTGCTGTGCTATGGAACACTGGGACT  
TCTTCCCTCTATCTAACTGTATATTTGTACCAGTTAACCAACCGTACTTCATCCCCACTC  
CTCTCTATCCTTCCCAACCTCTGATCACCTCATTTCTACTCTCTACCTCCATGAGATCCAC  
TTTTTTTAGCTCCACATGTGAGTAAGAAAATGCAATATTTGTCTTTCTGTGCCTGGCTTA  
TTTCACTTAACATAATGACTTCCTGTTCCATCCATGTTGCTGCAAATGACAGGATTTTCGT  
TCTTAATTTCAATTAAAATAACCACACATGGCAAAA

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## FIGURE 272

MGLLLLVLFLSLLPVAYTIMSLPPSFDCGPFRCRVSVAREHLPSRGSLLRGPRPRI PVLV  
SCQPVKGHGTLGESPMPPFKRVFCQDGNVRSFCVCAVHFSSHQPPVAVECLK

Important features of the protein:

Signal peptide:

amino acids 1-18

N-myristoylation site:

amino acids 86-92

Zinc carboxypeptidases, zinc-binding region 2 signature:

amino acids 68-79

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**FIGURE 273**

TTCTGAAGTAACGGAAGCTACCTTGTATAAAGACCTCAACACTGCTGACCATGATCAGCG  
CAGCCTGGAGCATCTTCCTCATCGGGACTAAAATTGGGCTGTTTCCTTCAAGTAGCACCTC  
TATCAGTTATGGCTAAATCCTGTCCATCTGTGTGTCGCTGCGATGCGGGTTTCATTTACT  
GTAATGATCGCTTTCTGACATCCATTCCAACAGGAATACCAGAGGATGCTACAACCTCTCT  
ACCTTCAGAACAACCAAATAAATAATGCTGGGATTCTTCAGATTTGAAAACTTGCTGA  
AAGTAGAAAGAATATACCTATACCACAACAGTTTAGATGAATTCCTACCAACCTCCCAA  
AGTATGTAAAAGAGTTACATTTGCAAGAAAATAACATAAGGACTATCACTTATGATTAC  
TTTCAAAAATTCCCTATCTGGAAGAATTACATTTAGATGACAACCTCTGTCTCTGCAGTTA  
GCATAGAAGAGGGAGCATTCCGAGACAGCAACTATCTCCGACTGCTTTTCCTGTCCCGTA  
ATCACCTTAGCACAAATTCCTGGGGTTTGCCAGGACTATAGAAGAACTACGCTTGATG  
ATAATCGCATATCCACTATTTTCATCACCATCTCTTCAAGGTCTCACTAGTCTAAAACGCC  
TGGTTCTAGATGGAAACCTGTTGAACAATCATGGTTTAGGTGACAAAGTTTTCTTCAACC  
TAGTTAATTTGACAGAGCTGTCCCTGGTGCGGAATTCCTGACTGCTGCACCAGTAAACC  
TTCCAGGCACAAACCTGAGGAAGCTTTATCTTCAAGATAACCACATCAATCGGGTGCCCC  
CAAATGCTTTTTCTTATCTAAGGCAGCTCTATCGACTGGATATGTCCAATAATAACCTAA  
GTAATTTACCTCAGGGTATCTTTGATGATTTGGACAATATAACACAACCTGATTCTTCGCA  
ACAATCCCTGGTATTGCGGGTGCAAGATGAAATGGGTACGTGACTGGTTACAATCACTAC  
CTGTGAAGGTCAACGTGCGTGGGCTCATGTGCCAAGCCCCAGAAAAGGTTCTGTTGGATGG  
CTATTAAGGATCTCAATGCAGAACTGTTTGATTGTAAGGACAGTGGGATTGTAAGCACCA  
TTCAGATAACCACTGCAATACCCAACACAGTGTATCCTGCCCAAGGACAGTGGCCAGCTC  
CAGTGACCAACAGCCAGATATTAAGAACCCCAAGCTCACTAAGGATCAACAAACCACAG  
GGAGTCCCTCAAGAAAAACAATTACAATTACTGTGAAGTCTGTACCTCTGATACCATTCT  
ATATCTCTTGGAACCTTGCTCTACCTATGACTGCTTTGAGACTCAGCTGGCTTAAACTGG  
GCCATAGCCCGGCATTTGGATCTATAACAGAAACAATTGTAACAGGGGAACGCAGTGAGT  
ACTTGGTCAACAGCCCTGGAGCCTGATTACCCCTATAAAGTATGCATGGTTCCCATGGAAA  
CCAGCAACCTCTACCTATTTGATGAAACTCCTGTTTGTATTGAGACTGAACTGCACCCC  
TTCGAATGTACAACCTACAACCACCCTCAATCGAGAGCAAGAGAAAGAACCTTACAAAA  
ACCCCAATTTACCTTTGGCTGCCATCATTTGGTGGGGCTGTGGCCCTGGTTACCATTGCCC  
TTCTTGCTTTAGTGTGTTGGTATGTTTCATAGGAATGGATCGCTCTTCTCAAGGAACTGTG  
CATATAGCAAAGGGAGGAGAAGAAAGGATGACTATGCAGAAGCTGGCACTAAGAAGGACA  
ACTCTATCCTGGAAATCAGGGAACTTCTTTTCAGATGTTACCAATAAGCAATGAACCCA  
TCTCGAAGGAGGAGTTTGTAAACACACCATATTTCTCCTAATGGAATGAATCTGTACA  
AAAACAATCACAGTGAAAGCAGTAGTAACCGAAGCTACAGAGACAGTGGTATTCCAGACT  
CAGATCACTCACACTCATGATGCTGAAGGACTCACAGCAGACTTGTGTTTTGGGTTTTTT  
AAACCTAAGGGAGGTGATGGT

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**FIGURE 274**

MISAAWSIFLIGTKIGLFLQVAPLSVMAKSCPSVCRC DAGFIYCND RFLTSIPTGIPEDA  
TTLYLQNNQINNAGIPSDLKNLLKVERIYLYHNSLDEFPTNLPKYVKELHLQENNIRTTIT  
YDSLSKIPLYLEELHLD DNSVSAVSI EEGAFRDSNYLRL LFLSRNHLSTIPWGLPRTIEEL  
RLDDNRISTISSPSLQGLTSLKRLVLDGNLLNNHGLGDKVFFNLVNLTELSLVRNSLTAA  
PVNLPGTNLRKLYLQDNHINRVPPNAFSYLRQLYRLDMSNNNLSNLPQGIFDDL DNITQL  
ILRNNPWYCGCKMKWVRDWLQSLPVKVNVRGLMCQAPEKVRGMAIKDLNAELFDCKDSGI  
VSTIQITTAIPNTVYPAQGGWPAPVTKQPD IKNPKLT KDQQTGSPSRKTITITVKS VTS  
DTIHISWKLALPMTALRLSWLKLGHSPAFGSITETIVTGERSEYLVTALEPDSPYKVC MV  
PMETSNLYLFDETPVCIETETAPLRMYNPTTTLNREQEKEPYKNPNLPLAAIIGGAVALV  
TIALLLALVCWYVHRNGSLFSRNCAYSKGRRRKDDYAEAGTKKDNSILEIRETSFQMLPIS  
NEPISKEEFVIHTIFPPNGMNL YKNNHSESSNRSYRDSGIPDS DSHSHS

**Important features of the protein:****Signal peptide:**

amino acids 1-28

**Transmembrane domain:**

amino acids 531-552

**N-glycosylation sites:**

amino acids 226-229, 282-285, 296-299, 555-558, 626-629, 633-636

**Tyrosine kinase phosphorylation site:**

amino acids 515-522

**N-myristoylation sites:**

amino acids 12-17, 172-177, 208-213, 359-364, 534-539, 556-561, 640-645

**Amidation site:**

amino acids 567-570

**Leucine zipper pattern:**

amino acids 159-180

**Phospholipase A2 aspartic acid active site:**

amino acids 34-44



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**FIGURE 275**

AGGGCCCCGCGGGTGGAGAGAGCGACGCCCCGAGGGGATGGCGGCAGCGTCCCGGAGCGCCT  
CTGGCTGGGCGCTACTGCTGCTGGTGGCACTTTGGCAGCAGCGCGCGGCCGGCTCCGGCG  
TCTTCCAGCTGCAGCTGCAGGAGTTCATCAACGAGCGCGGCGTACTGGCCAGTGGGCGGC  
CTTGCGAGCCCCGGCTGCCGACTTCTTCCGCGTCTGCCTTAAGCACTTCCAGGCGGTCTG  
TCTCGCCCCGACCCCTGCACCTTCGGGACCGTCTCCACGCCGGTATTGGGCACCAACTCCT  
TCGCTGTCCGGGACGACAGTAGCGGCGGGGGCGCAACCCTCTCCAAGTCCCTTCAATT  
TCACCTGGCCGGGTACCTTCTCGCTCATCATCGAAGCTTGGCACGCGCCAGGAGACGACC  
TGCGGCCAGAGGCCTTGCCACCAGATGCACTCATCAGCAAGATCGCCATCCAGGGCTCCC  
TAGCTGTGGGTGAGAACTGGTTATTGGATGAGCAAACCAGCACCCCTCACAAGGCTGCGCT  
ACTCTTACCGGGTCACTGTCAGTGACAACTACTATGGAGACAACTGCTCCCGCCTGTGCA  
AGAAGCGCAATGACCACTTCGGCCACTATGTGTGCCAGCCAGATGGCAACTTGTCTGCC  
TGCCCCGGTTGGACTGGGGAATATTGCCAACAGCCCTATCTGTCTTTCGGGCTGTATGAAC  
AGAATGGCTACTGCAGCAAGCCAGCAGAGTGCCTCTGCCGCCAGGCTGGCAGGGCCGGC  
TGTGTAACGAATGCATCCCCACAATGGCTGTGCCACGGCACCTGCAGCACTCCCTGGC  
AATGTACTTGTGATGAGGGCTGGGGAGGCCTGTTTTGTGACCAAGATCTCAACTACTGCA  
CCCACCACTCCCCATGCAAGAATGGGGCAACGTGCTCCAACAGTGGGCAGCGAAGCTACA  
CCTGCACCTGTGCGCCAGGCTACACTGGTGTGACTGTGAGCTGGAGCTCAGCGAGTGTG  
ACAGCAACCCCTGTGCAATGGAGGCAGCTGTAAGGACCAGGAGGATGGCTACCACTGCC  
TGTGTCTCCGGGCTACTATGGCCTGCACTGTGAACACAGCACCTTGAGCTGCGCCGACT  
CCCCCTGCTTCAATGGGGGCTCCTGCCGGGAGCGCAACCAGGGGGCCAACTATGCTTGTG  
AATGTCCCCCAACTTCACCGGCTCCAAGTGCAGAGAAGAAAGTGGACAGGTGCACCAGCA  
ACCCCTGTGCCAACGGGGGACAGTGCCTGAACCGAGGTCCAAGCCGCATGTGCCGCTGCC  
GTCCTGGATTACGGGCACCTACTGTGAACCTCCACGTCAGCGACTGTGCCCGTAACCTT  
GCGCCACGGTGGCACTTGCCATGACCTGGAGAATGGGCTCATGTGCACCTGCCCTGCCG  
GCTTCTCTGGCCGACGCTGTGAGGTGCGGACATCCATCGATGCCTGTGCCTCGAGTCCCT  
GCTTCAACAGGGCCACCTGCTACACCGACCTCTCCACAGACACCTTTGTGTGCAACTGCC  
CTTATGGCTTTGTGGGCAGCCGCTGCGAGTTCCCCGTGGGCTTGCCGCCAGCTTCCCCT  
GGGTGGCCGTCTCGCTGGGTGTGGGGCTGGCAGTGTGCTGGTACTGCTGGGCATGGTGG  
CAGTGGCTGTGCGGCAGCTGCGGCTTCGACGGCCGGACGACGGCAGCAGGGAAGCCATGA  
ACAACTTGTGCGGACTTCCAGAAGGACAACCTGATTCTGCGCGCCAGCTTAAAAACACAA  
ACCAGAAGAAGGAGCTGGAAGTGGACTGTGGCCTGGACAAGTCCAAGTGTGGCAAACAGC  
AAAACCACACATTGGACTATAATCTGGCCCCAGGGCCCCCTGGGGCGGGGGACCATGCCAG  
GAAAGTTTCCCACAGTGACAAGAGCTTAGGAGAGAAGGCGCCACTGCGGTTACACAGTG  
AAAAGCCAGAGTGTGCGATATCAGCGATATGCTCCCCAGGGACTCCATGTACCAGTCTG  
TGTGTTTGATATCAGAGGAGAGGAATGAATGTGTCAATTGCCACGGAGGTATAAGGCAGGA  
GCCTACCTGGACATCCCTGCTCAGCCCCGCGCTGGACCTTCCTTCTGCATTGTTTACA

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**FIGURE 276**

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCPEPGCRTFFRV  
CLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSSGGGRNPLQLPFNFTWPGTFSLIIE  
AWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTRLRYSYRVICSDNYY  
GDNC SRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYCSKPAECL  
CRPGWQGRLCNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC  
SNSGQRSYTCTCRPGYTGVDCLELSECDSNPCRNNGSCKDQEDGYHCLCPPGYGLHCE  
HSTLSCADSPCFNGGSCRERNQGANYACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNR  
GPSRMCRCRPGFTGT YCELHVSDCARNPCA HGGTCHDLENGLMCTCPAGFSGRRCEVRTS  
IDACASSPCFN RATCYTDLSTDTFVCNCPYGFVGSRCFPVGLPPSFPWVAVSLGVGLAV  
LLVLLGMVAVAVRQLRLRRPDDGSREAMNNLSDFQKDNLI PAAQLKNTNQKKELEVDCGL  
DKSNC GKQQNHTLDYNLAPGPLGRGTMPGKFP HSDKSLGEKAPLR LHSEKPECRISAICS  
PRDSMYQSVCLISEERNECVIATEV

**Important features of the protein:****Signal peptide:**

amino acids 1-26

**Transmembrane domain:**

amino acids 530-552

**N-glycosylation sites:**amino acids 108-112, 183-187, 205-209, 393-397, 570-574,  
610-614**Glycosaminoglycan attachment site:**

amino acids 96-100

**Tyrosine kinase phosphorylation site:**

amino acids 340-347

**N-myristoylation sites:**amino acids 42-48, 204-210, 258-264, 277-283, 297-303,  
383-389, 415-421, 461-467, 522-528, 535-541, 563-569,  
599-605, 625-631**Amidation site:**

amino acids 471-475

**Aspartic acid and asparagine hydroxylation site:**

amino acids 339-351

**EGF-like domain cysteine pattern signature:**amino acids 173-185, 206-218, 239-251, 270-282, 310-322,  
348-360, 388-400, 426-438, 464-476, 506-518**Calcium-binding EGF-like:**amino acids 224-245, 255-276, 295-316, 333-354, 373-394,  
411-432, 440-452

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**FIGURE 277**

GGCAGTGCAGCCGCCTCACAGGTCGGCGGACGGGGCCAGGCGGGCGGCCTCCTGAACCGAA  
CCGAATCGGCTCCTCGGGCCGTCGTCTCTCCCGCCCCCTCCTCGCCCCGCCCGGAGTTTTC  
TTTCGGTTTCTTCCAAGATTCTTGGCCTTCCCTCGACGGAGCCGGGCCCAGTGCGGGGGC  
GCAGGGCGCGGGAGCTCCACCTCCTCGGCTTTCCCTGCGTCCAGAGGCTGGCATGGCGCG  
GGCCGAGTACTGAGCGCACGGTCGGGGCACAGCAGGGCCGGGGGGTGCAGCTGGCTCGCG  
CCTCCTCTCCGGCCGCGTCTCCTCCGGTCCCTGGCGAAAGCCATTGAGACACCAGCTGG  
ACGTACGCGCGCGGAGCATGTCTGGGAGTCAGAGCGAGGTGGCTCCATCCCCGCAGAGTC  
CGCGGAGCCCCGAGATGGGACGGGACTTGCGGCCCGGGTCCCGCGTGCTCCTGCTCCTGC  
TTCTGCTCCTGCTGGTGTACCTGACTCAGCCAGGCAATGGCAACGAGGGCAGCGTCACTG  
GAAGTTGTTATTGTGGTAAAAGAATTTCTTCCGACTCCCCGCCATCGGTTCACTTCATGA  
ATCGTCTCCGGAAACACCTGAGAGCTTACCATCGGTGTCTATACTACACGAGGTTCCAGC  
TCCTTTCTGGAGCGTGTGTGGGGGCAACAAGGACCCATGGGTTCAGGAATTGATGAGCT  
GTCTTGATCTCAAAGAATGTGGACATGCTTACTCGGGGATTGTGGCCCACCAGAAGCATT  
TACTTCTTACCAGCCCCCAATTTCTCAGGCCTCAGAGGGGGCATCTTCAGATATCCACA  
CCCCTGCCCAGATGCTCCTGTCCACCTTGCACTCCACTCAGCGCCCCACCCTCCCAGTAG  
GATCACTGTCTCGGACAAAGAGCTCACTCGTCCCAATGAAACCACCATTACACTGCGG  
GCCACAGTCTGGCAGCTGGGCCTGAGGCTGGGGAGAACCAGAAGCAGCCGGAAAAAATG  
CTGGTCCCACAGCCAGGACATCAGCCACAGTGCCAGTCCTGTGCCTCCTGGCCATCATCT  
TCATCCTCACCGCAGCCCTTTCTTATGTGCTGTGCAAGAGGAGGAGGGGGCAGTCACCGC  
AGTCCTCTCCAGATCTGCCGGTTCATTATATACCTGTGGCACCTGACTCTAATACCTGAG  
CCAAGAATGGAAGCTTGTGAGGGTAAACTGTGGCTTATTCTTACAAAAAGTGTAAATAAAG  
GAGACTGACCCCTGACAACATGGTAGGCACTGTAAAAA

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**FIGURE 278**

MGRDLRPGSRVLLLLLLLLLVYLTQPGNGNEGSVTGSCYCGKRISSDSPPSVQFMNRLRK  
HLRAYHRCLYYTRFQLLSWSVCGGNKDPWVQELMSCLDLKECGHAYSGIVAHQKHLPTS  
PPISQASEGASSDIHTPAQMLLSTLQSTQRPTLPVGSLSSEKELTRPNETTIHTAGHSLA  
AGPEAGENQKQPEKNAGPTARTSATVPVLCCLAIIFILTAALSYVLCKRRRGQSPQSSPD  
LPVHYIPVAPDSNT

**Important features of the protein:**

**Signal peptide:**

1-26

**Transmembrane domain:**

204-223

**N-glycosylation site:**

168-172

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

42-46

**N-myristoylation site:**

29-35, 32-38, 36-42, 156-162

**Amidation site:**

40-44

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**FIGURE 279**

CGCGAGGCGCGGGGAGCCTGGGACCAGGAGCGAGAGCCGCTACCTGCAGCCGCCGCCCA  
CGGCACGGCAGCCACCCATGGCGCTCCTGCTGTGCTTCGTGCTCCTGTGCGGAGTAGTGGA  
TTTCGCCAGAAGTTTGTAGTATCACTACTCCTGAAGAGATGATTGAAAAAGCCAAAGGGGA  
AACTGCCTATCTGCCATGCAAATTTACGCTTAGTCCCGAAGACCAGGGACCGCTGGACAT  
CGAGTGGCTGATATCACCAGCTGATAATCAGAAGGTGGATCAAGTGATTATTTTATATTCT  
TGGAGACAAAATTTATGATGACTACTATCCAGATCTGAAAGGCCGAGTACATTTTACGAG  
TAATGATCTCAAATCTGGTGATGCATCAATAAATGTAACGAATTTACAACGTGCAGATAT  
TGGCACATATCAGTGCAAAGTGAAAAAGCTCCTGGTGTTGCAAATAAGAAGATTCATCT  
GGTAGTTCTTGTTAAGCCTTCAGGTGCGAGATGTTACGTTGATGGATCTGAAGAAATTGG  
AAGTGACTTTAAGATAAAATGTGAACCAAAAGAAGGTTCACTTCCATTACAGTATGAGTG  
GCAAAAATTGTCTGACTCACAGAAAATGCCACTTCATGGTTAGCAGAAATGACTTCATC  
TGTTATATCTGTAAAAAATGCCTCTTCTGAGTACTCTGGGACATACAGCTGTACAGTCAG  
AAACAGAGTGGGCTCTGATCAGTGCCCTGTTGCGTCTAAACGTTGTCCCTCCTTCAAATAA  
AGCTGGACTAATTGCAGGAGCCATTATAGGAACTTTGCTTGCTCTAGCGCTCATTGGTCT  
TATCATCTTTTGCTGTCTGTAAAAAGCGCAGAGAAGAAAAATATGAAAAGGAAGTTCATCA  
CGATATCAGGGAAGATGTGCCACCTCCAAAGAGCCGTACGTCCACTGCCAGAAGCTACAT  
CGGCAGTAATCATTCATCCCTGGGGTCCATGTCTCCTTCCAACATGGAAGGATATTCCAA  
GACTCAGTATAACCAAGTACCAAGTGAAGACTTTGAACGCACTCCTCAGAGTCCGACTCT  
CCCACCTGCTAAGTTCAAGTACCCTTACAAGACTGATGGAATTACAGTTGTATAAATATG  
GACTACTGAAGAATCTGAAGTATTGTATTATTTGACTTTATTTTAGGCCTCTAGTAAAGA  
CTTAAATGTTTTTTAAAAAAGCACAAAGGCACAGAGATTAGAGCAGCTGTAAGAACACAT  
CTACTTTATGCAATGGCATTAGACATGTAAGTCAGATGTCATGTCAAAATTAGTACGAGC  
CAAATTCCTTTGTTAAAAAACCTATGTATAGTGACACTGATAGTTAAAAGATGTTTTATT  
ATATTTTCAATAACTACCACTAACAAATTTTTTAACCTTTTCATATGCATATTTCTGATATGT  
GGTCTTTTAGGAAAAGTATGGTTAATAGTTGATTTTTTCAAAGGAAATTTTAAAATTCCTTA  
CGTTCGTGTTAATGTTTTTGCTATTTAGTTAAATACATTGAAGGGAAATACCCGTTCTTT  
TCCCCTTTTATGCACACAACAGAAACACGCGTTGTCATGCCTCAAACATTTTTTTATTTG  
CAACTACATGATTTACACAATTCCTTAAACAACGACATAAAATAGATTTCCCTGTATA  
TAAATAACTTACATACGCTCCATAAAGTAAATTCCTCAAAGGTGCTAGAACAAATCGTCCA  
CTTCTACAGTGTTCTCGTATCCAACAGAGTTGATGCACAATATATAAATACTCAAGTCCA  
ATATTA AAAA ACTTAGGCACCTTGACTA ACTTTAATAAAATTTCTCAAACATATCAATATC  
TAAAGTGCATATATTTTTTAAAGAAAGATTATTCTCAATAACTTCTATAAAAAATAAGTTTG  
ATGGTTTGGCCCATCTAACTTCACTACTATTAGTAAGAACTTTTAACTTTTAAATGTGTAG  
TAAGGTTTATTCTACCTTTTTCTCAACATGACACCAACACAATCAAAAACGAAGTTAGTG  
AGGTGCTAACATGTGAGGATTAATCCAGTGATTCCGGTCACAATGCATTCCAGGAGGAGG  
TACCCATGTCACTGGAATTGGGCGATATGGTTTATTTTTTCTTCCCTGATTTGGATAACC  
AAATGGAACAGGAGGAGGATAGTGATTCTGATGGCCATTCCCTCGATACATTCTTGGCTT  
TTTTCTGGGCAAAGGTGCCACATTGGAAGAGGTGGAAATATAAGTTCTGAAATCTGTAG  
GGAAGAGAACACATTAAGTTAATTCAAAGGAAAAAATCATCATCTATGTTCCAGATTTCT  
CATTAAGACAAAGTTACCCACAACACTGAGATCACATCTAAGTGACACTCCTATTGTCA  
GGTCTAAATACATTAAAAACCTCATGTGTAATAGGCGTATAATGTATAACAGGTGACCAA  
TGTTTTCTGAATGCATAAAGAAATGAATAAACTCAAACACAGTACTTCCTAAACAACTTC  
AACCAAAAAAGACCAAAACATGGAACGAATGGAAGCTTGTAAGGACATGCTTGTTTTAGT  
CCAGTGGTTTCCACAGCTGGCTAAGCCAGGAGTCACTTGGAGGCTTTTAAATACAAAACA  
TTGGAGCTGGAGGCCATTATCCTTAGCAAACCTAATGCAGAAACAGAAAATCAACTACCGC  
ATGTTCTCACTTATAAGTGGGAGGTAATGATAAGAACTTATGAACACAAAGAAGGAAACA  
ATAGACATTGGAGTCTATTTGAGAGGGGAGGGTGGGAGAAGGAAAAGGAGCAGAAAAGAT  
AACTATTGAGTACTGCCTTCACACCTGGGTGATGAAATAATATGTACAACAAATCCCTGT  
GACACATGTTTACCTATGGAACAAACCTTCATGTGTATCCCTAAACCTAAATAAAAGTT

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**FIGURE 280**

MALLLCFVLLCGVVDFARSLSTTTPEEMIEKAKGETAYLPCKFTLSPEDQGPLDIEWLIS  
PADNQKVDQVIILYSGDKIYDDYYPDLKGRVHFTSNDLKSGDASINVTNLQLSDIGTYQC  
KVKKAPGVANKKIHLVVLVKPSGARCIVDVGSEEIGSDFKIKCEPKEGSLPQYEWQKLS  
SQKMPTSWLAEMTSSVISVKNASSEYSGTYSCTVRNRVGSQCLLRNLNVPPSNKAGLIA  
GAIIGTLLALALIGLIIFCCRKKRREEKYEKEVHHDIREDVPPPKSRTSTARSYIGSNHS  
SLGSMSPSNMEGYSKTQYNQVPSEDFERTPQSPTLPPAKFKYPYKTDGITVV

**Signal sequence.**

amino acids 1-19

**Transmembrane domain:**

amino acids 236-257

**N-glycosylation sites:**

amino acids 106-110, 201-205, 298-302

**Tyrosine kinase phosphorylation sites:**

amino acids 31-39, 78-85, 262-270

**N-myristoylation sites:**amino acids 116-122, 208-214, 219-225, 237-243, 241-247,  
245-251, 296-302**Myelin P0 protein:**

amino acids 96-125

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**FIGURE 281**

TGCATCAGTGCCCAGGCAAGCCCAGGAGTTGACATTTCTCTGCCCAGCCATGGGCCTCAC  
CCTGCTCTTGCTGCTGCTCCTGGGACTAGAAGGTCAGGGCATAGTTGGCAGCCTCCCTGA  
GGTGCTGCAGGCACCCGTGGGAAGCTCCATTCTGGTGTCAGTGCCACTACAGGCTCCAGGA  
TGTCAAAGCTCAGAAGGTGTGGTGCCGGTTCTTGCCGGAGGGGTGCCAGCCCCCTGGTGTC  
CTCAGCTGTGGATCGCAGAGCTCCAGCGGGCAGGCGTACGTTTCTCACAGACCTGGGTGG  
GGGCCTGCTGCAGGTGGAAATGGTTACCCTGCAGGAAGAGGATGCTGGCGAGTATGGCTG  
CATGGTGATGGGGCCAGGGGGCCCCAGATTTTGACAGAGTCTCTCTGAACATACTGCC  
CCCAGAGGAAGAAGAAGAGACCCATAAGATTGGCAGTCTGGCTGAGAACGCATTCTCAGA  
CCCTGCAGGCAGTGCCAACCCCTTTGGAACCCAGCCAGGATGAGAAGAGCATCCCCCTTGAT  
CTGGGGTGCTGTGCTCCTGGTAGGTCTGCTGGTGGCAGCGGTGGTGCTGTTTGCTGTGAT  
GGCCAAGAGGAAACAAGAATCCCTCCTCAGTGGTCCACCACGTCAGTGACTCTGGACCGG  
CTGCTGAATTGCCTTTGGATGTACCACACATTAGGCTTGACTCACCACCTTCATTTGACA  
ATACCACCTACACCAGCCTACCTCTTGATTCCCCATCAGGAAAACCTTCACTCCCAGCTC  
CATCCTCATTTGCCCCCTCTACCTCCTAAGGTCCTGGTCTGCTCCAAGCCTGTGACATATG  
CCACAGTAATCTTCCCGGGAGGGAACAAGGGTGGAGGGACCTCGTGTGGGCCAGCCCAGA  
ATCCACCTAACAATCAGACTCCATCCAGCTAAGCTGCTCATCACACTTTAAACTCATGAG  
GACCATCCCTAGGGGTTCTGTGCATCCATCCAGCCAGCTCATGCCCTAGGATCCTTAGGA  
TATCTGAGCAACCAGGGACTTTAAGATCTAATCCAATGTCCTAACTTTACTAGGGAAAGT  
GACGCTCAGACATGACTGAGATGTCTTGGGGAAGACCTCCCTGCACCCAACTCCCCACT  
GGTTCTTCTACCATTACACACTGGGCTAAATAAACCTAATAATGATGTGCAAAAAAAAAA  
AA

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**FIGURE 282**

MGLTLLLLLLLLGLEGQGIVGSLPEVLQAPVGSSILVQCHYRLQDVKAQKVWCRFLPEGCQ  
PLVSSAVDRRAPAGRRTFLTDLGGGLLQVEMVTLQEEDAGEYGCMVDGARGPQILHRVSL  
NILPPEEEEEETHKIGSLAENAFSDPAGSANPLEPSQDEKSIPLIWGAVLLVGLLVAAVVL  
FAVMAKRKQESLLSGPPRQ

**Important features of the protein:**

**Signal peptide:**

amino acids 1-15

**Transmembrane domain:**

amino acids 161-181

**N-myristoylation sites:**

amino acids 17-23, 172-178

**Amidation site:**

amino acids 73-79



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**FIGURE 283**

GTAGCATAGTGTGCAGTTCACCTGGACCAAAAGCTTTGGCTGCACCTCTTCTGGAAAGCTG  
GCCATGGGGCTCTTCATGATCATTGCAATTCTGCTGTTCCAGAAACCCACAGTAACCGAA  
CAACTTAAGAAGTGCTGGAATAACTATGTACAAGGACATTGCAGGAAAATCTGCAGAGTA  
AATGAAGTGCCTGAGGCACTATGTGAAAATGGGAGATACTGTTGCCTCAATATCAAGGAA  
CTGGAAGCATGTAAAAAATTACAAAGCCACCTCGTCCAAAGCCAGCAACACTTGCACTG  
ACTCTTCAAGACTATGTTACAATAATAGAAAATTTCCCAAGCCTGAAGACACAGTCTACA  
TAAATCAAATACAATTTCTGTTTTCACTTGCTTCTCAACCTAGTCTAATAAACTAAGGTGA  
TGAGATATACATCTTCTTCTTCTGGTTTCTTGATCCTTAAAATGACCTTCGAGCATATT  
CTAATAAAGTGCATTGCCAGTTAAAAA

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## FIGURE 284

MGLFMIIAILLFQKPTVTEQLKKCWNNYVQGHCRKICRVNEVPEALCENGRYCCLNIKEL  
EACKKITKPPRPKPATLALTLDYVTIIENFPSLKTQST

Important features of the protein:

Signal peptide:

None

Transmembrane domain:

None

cAMP- and cGMP-dependent protein kinase phosphorylation site:

64-68

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**FIGURE 285**

GATGGCGCAGCCACAGCTTCTGTGAGATTTCGATTTCTCCCCAGTTCCCCTGTGGGTCTGA  
GGGGACCAGAAGGGTGAGCTACGTTGGCTTTCTGGAAGGGGAGGCTATATGCGTCAATTC  
CCCCAAAACAAGTTTGTGACATTTCCCCTGAAATGTCATTCTCTATCTATTCAGTCAAGTG  
CCTGCTGTTCCAGGCCTTACCTGCTGGGCACTAACGGCGGAGCCAGGATGGGGACAGAAT  
AAAGGAGCCACGACCTGTGCCACCAACTCGCACTCAGACTCTGAACTCAGACCTGAAATC  
TTCTCTTCACGGGAGGCTTGGCAGTTTTTCTTACTCCTGTGGTCTCCAGATTTCAGGCCT  
AAGATGAAAGCCTCTAGTCTTGCCCTTCAGCCTTCTCTCTGCTGCGTTTTATCTCCTATGG  
ACTCCTTCCACTGGACTGAAGACACTCAATTTGGGAAGCTGTGTGATCGCCACAAACCTT  
CAGGAAATACGAAATGGATTTTCTGAGATACGGGGCAGTGTGCAAGCCAAAGATGGAAAC  
ATTGACATCAGAATCTTAAGGAGGACTGAGTCTTTGCAAGACACAAAGCCTGCGAATCGA  
TGCTGCCTCCTGCGCCATTTGCTAAGACTCTATCTGGACAGGGTATTTAAAACTACCAG  
ACCCCTGACCATTATACTCTCCGGAAGATCAGCAGCCTCGCCAATTCCTTTCTTACCATC  
AAGAAGGACCTCCGGCTCTCTCATGCCCACATGACATGCCATTGTGGGGAGGAAGCAATG  
AAGAAATACAGCCAGATTCTGAGTCACTTTGAAAAGCTGGAACCTCAGGCAGCAGTTGTG  
AAGGCTTTGGGGGAAGTAGACATTCTTCTGCAATGGATGGAGGAGACAGAATAGGAGGAA  
AGTGATGCTGCTGCTAAGAATATTCGAGGTCAAGAGCTCCAGTCTTCAATACCTGCAGAG  
GAGGCATGACCCCAAACCACCATCTCTTTACTGTACTAGTCTTGTGCTGGTCACAGTGTA  
TCTTATTTATGCATTACTTGCTTCCTTGCATGATTGTCTTTATGCATCCCCAATCTTAAT  
TGAGACCATACTTGTATAAGATTTTGTAAATATCTTTCTGCTATTGGATATATTTATTAG  
TTAATATATTTATTTATTTTGTCTATTTAATGTATTTATTTTTTTACTTGGACATGAAA  
CTTTAAAAAAATTCACAGATTATATTTATAACCTGACTAGAGCAGGTGATGTATTTTTAT  
ACAGTAAAAAAAACCTTGTAATTCAGAAAGAGTGGCTAGGGGGGTATTTCATTTG  
TATTCAACTAAGGACATATTTACTCATGCTGATGCTCTGTGAGATATTTGAAATTGAACC  
AATGACTACTTAGGATGGGTTGTGGAATAAGTTTTGATGTGGAATTGCACATCTACCTTA  
CAATTACTGACCATCCCCAGTAGACTCCCCAGTCCCATAATTGTGTATCTTCCAGCCAGG  
AATCCTACACGGCCAGCATGTATTTCTACAAATAAAGTTTTCTTGCATACCAAAAAAAA  
AAAAAAA

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## FIGURE 286

MKASSLAFSLLSAAFYLLWTPSTGLKTLNLGSCVIATNLQEIRNGFSEIRGSVQAKDGN  
DIRILRRTESLQDTKPANRCCLLRHLLRLYLDRVFKNYQTPDHYTLRKISSLANSLTIK  
KDLRLSHAHMTCHCGEEAMKKYSQILSHFEKLEPQAAVVKALGELDILLQWMEETE

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**FIGURE 287**

AATGCCCCATGCGCACCCACAGCTCGCGCTCCTGCAAGTGTTCTTTCTGGTGTTCCTCG  
ATGGCGTCCGGCCTCAGCCCTCTTCCTCCCCATCAGGGGCAGTGCCACGTCTTTGGAGC  
TGCAGCGAGGGACGGATGGCGGAACCTCCAGTCCCCTTCAGAGGCGACTGCAACTCGCC  
CGGCCGTGCCTGGACTCCCTACAGTGGTCCCTACTCTCGTGACTCCCTCGGCCCCCTGGGA  
ATAGGACTGTGGACCTCTTCCCAGTCTTACCGATCTGTGTCTGTGACTTGACTCCTGGAG  
CCTGCGATATAAATTGCTGCTGCGACAGGGACTGCTATCTTCTCCATCCGAGGACAGTTT  
TCTCCTTCTGCCTTCCAGGCAGCGTAAGGTCTTCAAGCTGGGTTTGTGTAGACAACTCTG  
TTATCTTCAGGAGTAATTCCCCGTTTCCTTCAAGAGTTTTTCATGGATTCTAATGGAATCA  
GGCAGTTTTGTGTCCATGTGAACAACTCAAACCTTAAACTATTTCCAGAAGCTTCAAAGG  
TCAATGCAACCAACTTCCAGGCCCTGGCTGCAGAGTTTGGAGGCGAATCATTCACTTCAA  
CATTCCAACTCAATCACCACCATCTTTTTACAGGGCTGGGGACCCCATCTTACTTACT  
TCCCCAAGTGGTCTGTAATAAGCTTGCTGAGACAACTGCAGGAGTTGGAGCTGGGGGAC  
TCTGTGCTGAAAGCAATCCTGCAGGTTTCTTAGAGAGTAAAAGTACAACCTTGCACTCGTT  
TTTTCAAGAACCTGGCTAGTAGCTGTACCTTGGATTGAGCCCTCAATGCTGCCTCTTACT  
ATAACTTCACAGTCTTAAAGGTTCCAAGAAGCATGACTGATCCACAGAATATGGAGTTCC  
AGGTTCTGTAATACTTACCTCACAGGCTAATGCTCCTCTGTTGGCTGGAAACACTTGTC  
AGAATGTAGTTTCTCAGGTCACCTATGAGATAGAGACCAATGGGACTTTTGGAATCCAGA  
AAGTTTCTGTGAGTTTGGGACAAACCAACCTGACTGTTGAGCCAGGCGCTTCTTACAGC  
AACACTTCATCCTTCGCTTCAGGGCTTTTCAACAGAGCACAGCTGCTTCTCTCACCAGTC  
CTAGAAGTGGGAATCCTGGCTATATAGTTGGGAAGCCACTCTTGGCTCTGACTGATGATA  
TAAGTTACTCAATGACCCTCTTACAGAGCCAGGGTAATGGAAGTTGCTCTGTTAAAAGAC  
ATGAAGTGCAGTTTGGAGTGAATGCAATATCTGGATGCAAGCTCAGGTTGAAGAAGGCAG  
ACTGCAGCCACTTGCAGCAGGAGATTTATCAGACTCTTCATGGAAGGCCAGACCAGAGT  
ATGTTGCCATCTTTGGTAATGCTGACCCAGCCAGAAAGGAGGGTGGACCAGGATCCTCA  
ACAGGCACTGCAGCATTTCAGCTATAAACTGTACTTCCTGCTGTCTCATAACAGTTTCCC  
TGGAGATCCAGGTATTGTGGGCATATGTAGGTCTCCTGTCCAACCCGCAAGCTCATGTAT  
CAGGAGTTCGATTCTTATACAGTGCCAGTCTATACAGGATTCTCAGCAAGTTACAGAAG  
TATCTTTGACAACTCTTGTGAACTTTGTGGACATTACCCAGAAGCCACAGCCTCCAAGGG  
GCCAACCCAAAATGGACTGGAAATGGCCATTGACTTCTTTCCCTTCAAAGTGGCATTCA  
GCAGAGGAGTATTCTCTCAAAAATGCTCAGTCTCTCCCATCCTTATCCTGTGCCTCTTAC  
TACTTGGAGTTCTCAACCTAGAGACTATGTGAAGAAAGAAAATAATCAGATTTAGTTT  
TCCCTATGAGAACTCTGAGGCAGCCACTTATCTTGGCTAAATAGAACCTCACCTGCTCA  
TGACCAGAGAGCATTTAGGATAATAGATGACCTAACTGAAGGAATCCTTGTATATGAAAG  
GAGTTATTTTAGAAAAGCAATAAAAATATTTTATTCATCNTAAAAAAAAA

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**FIGURE 288**

MRTPQLALLQVFFLVFPDGVPRQPSSSSPSGAVPTSLELQRGTDGGTLQSPSEATATRP  
PGLPTVVPTLVTPSAPGNRTVDLFPVLPICVCDLTPGACDINCCCDRDCYLLHPRTVFSF  
CLPGSVRSSSWVCVDNSVIFRSNSPFPSPRVFMDSNQIRQFCVHVNNNSLNYFQKLQKVNA  
TNFQALAAEFGGESFTSTFQTQSPPSFYRAGDPILTYFPKWSVISLLRQPAGVGAGGLCA  
ESNPAGFLESKSTTCTRFFKNLASSCTLDSALNAASYNFTVLKVPRSM TDPQNMEFQVP  
VILTSQANAPLLAGNTCQNVVSQVTYEIETNGTFGIQKVS VSLGQTNLTVEPGASLQQHF  
ILRFRAFQQSTAASLTSPRSGNPGYIVGKPLLALTDDISYSMTLLQSQNGSGCSVKRHEV  
QFGVNAISGCKLRLKKADCSHLQQEIYQTLHGRPRPEYVAIFGNADPAQKGGWTRILNRH  
CSISAINCTSCCLIPVSLEIQVLWAYVGLLSNPQAHVSGVRFLYQCQSIQDSQQVTEVSL  
TTLVNFDITQKPQPPRGQPKMDWKWPFDFPFKVAFSRGVFSQKCSVSPILILCLLLLG  
VLNLETM

**Important features of the protein:****Signal peptide:**

amino acids 1-22

**Transmembrane domains:**

amino acids 484-505, 581-600

**N-glycosylation sites:**amino acids 78-82, 165-169, 179-185, 279-285, 331-337,  
347-351, 410-414, 487-491**N-myristoylation sites:**

amino acids 30-36, 41-47, 124-130, 232-238, 236-242, 409-415

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 420-431

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**FIGURE 289**

CGCGGAGCCCTGCGCTGGGAGGTGCACGGTGTGCACGCTGGACTGGACCCCCATGCAACC  
CCGCGCCCTGCGCCTTAACCAGGACTGCTCCGCGCGCCCCTGAGCCTCGGGCTCCGGCCC  
GGACCTGCAGCCTCCAGGTGGCTGGGAAGAACTCTCCAACAATAAATACATTTGATAAG  
AAAGATGGCTTTAAAAGTGCTACTAGAACAGAGAAAACGTTTTTCACTCTTTTAGTATT  
ACTAGGCTATTTGTCTGTAAAGTGACTTGTGAATCAGGAGACTGTAGACAGCAAGAATT  
CAGGGATCGGTCTGGAACTGTGTTCCCTGCAACCAGTGTGGGCCAGGCATGGAGTTGTC  
TAAGGAATGTGGCTTCGGCTATGGGGAGGATGCACAGTGTGTGACGTGCCGGCTGCACAG  
GTTCAAGGAGGACTGGGGCTTCAGAAATGCAAGCCCTGTCTGGACTGCGCAGTGGTGAA  
CCGCTTTTCAAGAGGCAAATTGTTTCAGCCACCAGTGATGCCATCTGCGGGGACTGCTTGCC  
AGGATTTTATAGGAAGACGAACTTGTTCGGCTTTCAAGACATGGAGTGTGTGCCTTGTTGG  
AGACCTCTCTCTCTTACGAACCGCACTGTGCCAGCAAGGTCAACCTCGTGAAGATCGC  
GTCCACGGCCTCCAGCCCACGGGACACGGCGCTGGCTGCCGTTATCTGCAGCGCTCTGGC  
CACCGTCTGTGGCCCTGCTCATCTCTGTGTCTATCTATTGTAAGAGACAGTTTATGGA  
GAAGAAACCCAGCTGGTCTCTGCGGTGCGCAGGACATTCAGTACAACGGCTCTGAGCTGTC  
GTGTTTTGACAGACCTCAGCTCCACGAATATGCCACAGAGCCTGCTGCCAGTGCCGCCG  
TGACTCAGTGCAGACCTGCGGGCCGGTGCCTTGTCTCCATCCATGTGCTGTGAGGAGGC  
CTGCAGCCCCAACCCGGCGACTCTTGTTGTGGGGTGCATTCTGCAGCCAGTCTTCAGGC  
AAGAAACGCAGGCCAGCCGGGAGATGGTGCCGACTTCTTCGGATCCCTCACGCAGTC  
CATCTGTGGCGAGTTTTTCAGATGCCTGGCCTCTGATGCAGAATCCCATGGGTGGTGACAA  
CATCTCTTTTTGTGACTCTTATCTGAACCTCACTGGAGAAGACATTCATTCTCTCAATCC  
AGAACTTGAAAGCTCAACGTCTTTTGATTCAAATAGCAGTCAAGATTTGTTGGTGGGGC  
TGTTCCAGTCCAGTCTCATTCTGAAAACCTTACAGCAGCTACTGATTTATCTAGATATAA  
CAACACACTGGTAGAATCAGCATCAACTCAGGATGCACTAACTATGAGAAGCCAGCTAGA  
TCAGGAGAGTGGCGCTGTCTATCCACCCAGCCACTCAGACGTCCCTCCAGGAAGCTTAAAG  
AACCTGCTTCTTTCTGCAGTAGAAGCGTGTGCTGGAACCCAAAGAGTACTCCTTTGTTAG  
GCTTATGGAAGTGCAGTCTGGACCTTGCATGGCTTCTGGGGCAAAAATAAATCTGAACC  
AACTGACGGCATTGTAAGCCTTTTCAGCCAGTTGCTTCTGAGCCAGACCAGCTGTAAGCT  
GAAACCTCAATGAATAACAAGAAAAGACTCCAGGCCGACTCATGATACTCTGCATCTTTC  
CTACATGAGAAGCTTCTCTGCCACAAAAGTGACTTCAAAGACTGATGGGTGAGCTGGCA  
GCCTATGAGATTGTGGACATATAACAAGAAACAGAAATGCCCTCATGCTTATTTTCATGG  
TGATTGTGGTTTTACAAGACTGAAGACCCAGAGTATACTTTTTCTTCCAGAAATAATTT  
CATACCGCTATGAAATATCAGATAAATTACCTTAGCTTTTATGTAGAATGGGTTCAAA  
GTGAGTGTCTTATTTGAGAAGGACACTTTTTTCATCATCTAACTGATTCGCATAGGTGG  
TTAGAATGGCCCTCATATTGCCTGCCTAAATCTTGGGTTTATTAGATGAAGTTTACTGAA  
TCAGAGGAATCAGACAGAGGAGGATAGCTCTTCCAGAATCCACACTTCTGACCTCAGCC  
TCGGTCTCATGAACACCCGCTGATCTCAGGAGAACACCTGGGCTAGGGAATGTGGTCGAG  
AAAGGGCAGCCCATGCCCAGAAATTAACACATATTGTAGAGACTTGTATGCAAAGGTTGG  
CATATTTATATGAAAATTAGTTGCTATAGAAACATTTGTTGCATCTGTCCCTCTGCCTGA  
GCTTAGAAGGTTATAGAAAAGGGTATTTATAAACATAAATGACCTTTTACTTGCATTGT  
ATCTTATACTAAAGGCTTTAGAAATTACAACATATCAGGTTCCCTACTACTGAAGTAGC  
CTTCCGTGAGAACACACCACATGTTAGGACTAGAAGAAAATGCACAATTTGTAGGGGTTT  
GGATGAAGCAGCTGTAACCTGCCCTAGTGTAGTTTGACCAGGACATTGTCTGTCTCCTTCC  
AATTGTGTAAGATTAGTTAGCACATCATCTCCTACTTTAGCCATCCGGTGTGGATTAA  
GAGGACGGTGCTTCTTTCTATTAAAGTGCTCCATCCCTACCATCTACACATTAGCATTG  
TCTCTAGAGCTAAGACAGAAATTAACCCCGTTTCAGTCAAAAGCAGGGAATGGTTCAATTT  
ACTCTTAATCTTTATGCCCTGGAGAAGACCTACTTGAACAGGGCATATTTTTTTAGACTTC  
TGAACATCAGTATGTTTCGAGGGTACTATGATATTTTGGTTTGAATTGCCCTGCCCAAGT  
CACTGTCTTTTAACTTTTAACTGAATATTAAATGTATCTGTCTTCT

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**FIGURE 290**

MALKVLLLEQEKTFFTLLVLLGYLSCKVTCESGDCRQQEFRDRSGNCVPCNQCGPGMELSK  
ECGFGYGEDAQCVTCLHHRFKEDWGFQKCKPCLDCAVVNRFOKANCSATSDAICGDCLPG  
FYRKTCLVGFQDMECVPCGDPPPPYEPHCASKVNLVKIASTASSPRDTALAAVICSALAT  
VLLALLILCVIYCKRQFMKKPSWSLSQDIQYNGSELSCFDRPQLHEYAHRACCQCRRD  
SVQTCGPVRLLLPSMCCEEACSPNPATLGCGVHSAASLQARNAGPAGEMVPTFFGSLTQSI  
CGEFSDAWPLMQNPMGGDNISFCDSYPELTGEDIHSLNPELESSTSLDSNSSQDLVGGAV  
PVQSHSENFTAATDLSRYNNTLVESASTQDALTMRSQLDQESGAVIHPATQTSLQEA

**Important features of the protein:****Signal peptide:**

Amino acids 1-25

**Transmembrane domain:**

Amino acids 169-192

**N-glycosylation sites:**

Amino acids 105-109; 214-218; 319-323; 350-354; 368-372; 379-383

**cAMP- and cGMP-dependent protein kinase phosphorylation sites:**

Amino acids 200-204; 238-242

**Tyrosine kinase phosphorylation site:**

Amino acids 207-214

**N-myristoylation sites:**

Amino acids 55-61; 215-221; 270-276

**Prokaryotic membrane lipoprotein lipid attachment site:**

Amino acids 259-270

**TNFR/NGFR family cysteine-rich region proteins:**

Amino acids 89-96



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**FIGURE 291**

CCTGGAGCCGGAAGCGCGGCTGCAGCAGGGCGAGGCTCCAGGTGGGGTTCGGTTCCGCATC  
CAGCCTAGCGTGTCACGATGCGGCTGGGCTCCGGGACTTTTCGCTACCTGTTGCGTAGCG  
ATCGAGGTGCTAGGGATCGCGGTCTTCCTTCGGGGATTCTTCCCGGCTCCCGTTCGTTCC  
TCTGCCAGAGCGGAACACGGAGCGGAGCCCCAGCGCCCGAACCCCTCGGCTGGAGCCAGT  
TCTAACTGGACCACGCTGCCACCACCTCTCTTCAGTAAAGTTGTTATTGTTCTGATAGAT  
GCCTTGAGAGATGATTTTGTGTTTGGGTCAAAGGGTGTGAAATTTATGCCCTACACAAC  
TACCTTGTGGAAAAAGGAGCATCTCACAGTTTGTGGCTGAAGCAAAGCCACCTACAGTT  
ACTATGCCTCGAATCAAGGCATTGATGACGGGGAGCCTTCCTGGCTTTGTGACGTCATC  
AGGAACCTCAATTCTCCTGCACTGCTGGAAGACAGTGTGATAAGACAAGCAAAAGCAGCT  
GGAAAAAGAATAGTCTTTTATGGAGATGAAACCTGGGTAAATTATTCCCAAAGCATTTT  
GTGGAATATGATGGAACAACCTCATTTTTCTGTGTCAGATTACACAGAGGTGGATAATAAT  
GTCACGAGGCATTTGGATAAAGTATTAAAAAGAGGAGATTGGGACATATTAATCCTCCAC  
TACCTGGGGCTGGACCACATTGGCCACATTTACAGGGCCCAACAGCCCCCTGATTGGGCAG  
AAGCTGAGCGAGATGGACAGCGTGCTGATGAAGATCCACACCTCACTGCAGTCGAAGGAG  
AGAGAGACGCCTTTACCCAATTTGCTGGTTCTTTGTGGTGACCATGGCATGTCTGAAACA  
GGAAGTCACGGGGCTCCTCCACCGAGGAGGTGAATACACCTCTGATTTTAATCAGTTCT  
GCGTTTGAAAGGAAACCCGGTGATATCCGACATCCAAAGCACGTCCAATAGACGGATGTG  
GCTGCGACACTGGCGATAGCACTTGCTTACCGATTCCAAAAGACAGTTGAGGAGCCTC  
CTATTCCAGTTGTGGAAGGAAGACCAATGAGAGAGCAGTTGAGATTTTACATTTGAAT  
ACAGTGCAGCTTAGTAAACTGTTGCAAGAGAATGTGCCGTATATGAAAAAGATCCTGGG  
TTTGAGCAGTTTAAATGTCAGAAAGATTGCATGGGAACTGGATCAGACTGTACTTGGAG  
GAAAAGCATTCAGAAAGTCTATTCAACCTGGGCTCCAAGGTTCTCAGGCAGTACCTGGAT  
GCTCTGAAGACGCTGAGCTTGTCCCTGAGTGCACAAGTGGCCCAGTTCTCACCCCTGCTCC  
TGCTCAGCGTCCACAGGCACTGCACAGAAAGGCTGAGCTGGAAGTCCACTGTCTCTC  
CTGGGTTTCTCTGCTCTTTTATTGTTGATCCTGGTTCTTTCGGCCGTTACCGTCATTG  
TGTGCACCTCAGCTGAAAGTTCGTGCTACTTCTGTGGCCTCTCGTGGCTGGCGGCAGGCT  
GCCTTTCGTTTACCAGACTCTGGTTGAACACCTGGTGTGTGCCAAGTGCTGGCAGTGCCC  
TGGACAGGGGGCCTCAGGGAAGGACGTGGAGCAGCCTTATCCAGGCCTCTGGGTGTCCC  
GACACAGGTGTTACATCTGTGCTGTGAGGTGAGTGCCTCAGTTCTTGAAAGCTAGGT  
TCCTGCGACTGTTACCAAGGTGATTGTAAAGAGCTGGCGGTACACAGAGGAACAAGCCCC  
CAGCTGAGGGGGTGTGTGAATCGGACAGCCTCCAGCAGAGGTGTGGGAGCTGCAGCTGA  
GGGAAGAAGAGACAATCGGCCTGGACACTCAGGAGGGTCAAAGGAGACTTGGTCGCACC  
ACTCATCCTGCCACCCCAAGATGCATCCTGCCTCATCAGGTCCAGATTTCTTCCAAGG  
CGGACGTTTCTGTTGGAATTCTTAGTCCTTGGCCTCGGACACCTTCATTCGTTAGCTGG  
GGAGTGGTGGTGAGGCAGTGAAGAAGAGGCGGATGGTCACACTCAGATCCACAGAGCCCA  
GGATCAAGGGACCCACTGCAGTGGCAGCAGGACTGTTGGGCCCCCAACCCCTGCAC  
AGCCCTCATCCCCTCTTGGCTTGAGCCGTCAGAGGCCCTGTGCTGAGTGTCTGACCGAGA  
CACTCACAGCTTTGTCTATCAGGGCACAGGCTTCCTCGGAGCCAGGATGATCTGTGCCACG  
CTTGCACCTCGGGCCCATCTGGGCTCATGCTCTCTCCTGCTATTGAATTAGTACCTAG  
CTGCACACAGTATGTAGTTACCAAAAGAATAAACGGCAATAATTGAGAAAAAAA

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**FIGURE 292**

MRLGSGTFATCCVAIEVLGIAVFLRGFFPAPVRSSARAEGHGAEPPEPSAGASSNWTTL  
PPPLFSKVIVLIDALRDDFVFGSKGVKFMPYTTYLVEKGASHSFVAEAKPPTVTMPRIK  
ALMTGSLPGFVDVIRNLNSPALLEDVIRQAKAAGKRIVFYGDETWVKLFPHFVEYDGT  
TSFFVSDYTEVDNNVTRHLDKVLKRGDWDILILHYLGLDGHIGHISGPNSPLIGQKLSEMD  
SVLMKIHTSLQSKERETPLPNLLVLCGDHGMSETGSHGASSTEEVNTPLILISSAFERKP  
GDIRHPKHVQ

**Important features of the protein:****Signal peptide:**

amino acids 1-34

**Transmembrane domain:**

amino acids 58-76

**N-glycosylation sites:**

amino acids 56-60, 194-198

**N-myristoylation sites:**amino acids 6-12, 52-58, 100-106, 125-131, 233-239, 270-276,  
275-281, 278-284**Amidation site:**

amino acids 154-158

**Cell attachment sequence:**

amino acids 205-208

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**FIGURE 293**

AGCCAGGCAGCACATCACAGCGGGAGGAGCTGTCCCAGGTGGCCCAGCTCAGCAATGGCA  
ATGGGGGTCCCCAGAGTCATTCTGCTCTGCCTCTTTGGGGCTGCGCTCTGCCTGACAGGG  
TCCCAAGCCCTGCAGTGCTACAGCTTTGAGCACACCTACTTTGGCCCCTTTGACCTCAGG  
GCCATGAAGCTGCCCAGCATCTCCTGTCTCATGAGTGCTTTGAGGCTATCCTGTCTCTG  
GACACCGGGTATCGCGCGCCGGTGACCCTGGTGCGGAAGGGCTGCTGGACCGGGCCTCCT  
GCGGGCCAGACGCAATCGAACCCGGACGCGCTGCCGCCAGACTACTCGGTGGTGCGCGGC  
TGCACAACTGACAAATGCAACGCCCACCTCATGACTCATGACGCCCTCCCCAACCTGAGC  
CAAGCACCCGACCCGCCGACGCTCAGCGGCGCCGAGTGCTACGCCTGTATCGGGGTCCAC  
CAGGATGACTGCGCTATCGGCAGGTCCCGACGAGTCCAGTGTCACCAGGACCAGACCGCC  
TGCTTCCAGGGCAGTGGCAGAATGACAGTTGGCAATTTCTCAGTCCCTGTGTACATCAGA  
ACCTGCCACCGGCCCTCCTGCACCACCGAGGGCACCACCAGCCCCTGGACAGCCATCGAC  
CTCCAGGGCTCCTGCTGTGAGGGGTACCTCTGCAACAGGAAATCCATGACCCAGCCCTTC  
ACCAGTGCTTCAGCCACCACCCCTCCCCGAGCACTACAGGTCCTGGCCCTGCTCCTCCCA  
GTCCTCCTGCTGGTGGGGCTCTCAGCATAGACCGCCCCTCCAGGATGCTGGGGACAGGGC  
TCACACACCTCATTCTTGCTGCTTCAGCCCCTATCACATAGCTCACTGGAAAATGATGTT  
AAAGTAAGAATTGCAAAA

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**FIGURE 294**

MAMGVPRVILLCLFGAALCLTGSQALQCYSFEHTYFGPFDLRAMKLPSISCPHECFEAIL  
SLDTGYRAPVTLVKGCWTGPPAGQTQSNPDALPPDYSVVRGCTTDKCNAHLMTHDALPN  
LSQAPDPPTLSGAECYACIGVHQDDCAIGRSRRVQCHQDQTACFQSGRMTVGNFSVPVY  
IRTCHRPSCCTTEGTTSPWTAIDLQSCCEGYLCNRKSMTQPFTSASATTPPRALQVLALL  
LPVLLLLVGLSA

**Important features of the protein:**

**Signal peptide:**

amino acids 1-19

**Transmembrane domain:**

amino acids 233-251

**N-glycosylation sites:**

amino acids 120-124, 174-178

**N-myristoylation sites:**

amino acids 15-21, 84-90

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**FIGURE 295**

AATCGGCTGATTCTGCATCTGGAACTGCCTTCATCTTGAAAGAAAAGCTCCAGGTCCCT  
TCTCCAGCCACCCAGCCCCAAGATGGTGATGCTGCTGCTGCTGCTTTCCGCACTGGCTGG  
CCTCTTCGGTGCGGCAGAGGGACAAGCATTTCATCTTGGAAGTGCCCCAATCCTCCGGT  
GCAGGAGAATTTTGACGTGAATAAGTATCTCGGAAGATGGTACGAAATTGAGAAGATCCC  
AACAACCTTTGAGAATGGACGCTGCATCCAGGCCAACTACTACTAATGGAAAACGGAAA  
GATCAAAGTGTTAAACCAGGAGTTGAGAGCTGATGGAAGTGTGAATCAAATCGAAGGTGA  
AGCCACCCAGTTAACCTCACAGAGCCTGCCAAGCTGGAAGTTAAGTTTTCTGGTTTAT  
GCCATCGGCACCGTACTGGATCCTGGCCACCGACTATGAGAACTATGCCCTCGTGATTTC  
CTGTACCTGCATCATCAACTTTTTTCACGTGGATTTTGCTTGGATCTTGGCAAGAAACCC  
TAATCTCCCTCCAGAAACAGTGGACTCTCTAAAAAATATCCTGACTTCTAATAACATTGA  
TGTCAAGAAAATGACGGTCACAGACCAGGTGAACTGCCCCAAGCTCTCGTAACCAGGTTTC  
TACAGGGAGGCTGCACCCACTCCATGTTACTTCTGCTTCGCTTTCCCCTACCCACCCCC  
CCCCCATAAAGACAAACCAATCAACCACGACAAAGGAAGTTGACCTGAACATGTAACCAT  
GCCCTACCCTGTTACCTTGCTAGCTGCAAAATAAACTTGTTGCTGACCTGCTGTGCTCGC  
AAAAAA

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**FIGURE 296**

MVMLLLLLLSALAGLFGAAEGQAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPTTFENG  
RCIQANYSLMENGKIKVLNQELRADGTVNQIEGEATPVNLTEPAKLEVKFSWFMPSPAY  
WILATDYENYALVYSCTCIIQLFHVDFAWILARNPNLPPETVDSLKNILTSNNIDVKKM  
TVTDQVNCPKLS

**Signal sequence:**

1-16

**N-glycosylation site:**

65-68

98-101

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

175-178

**N-myristoylation site:**

13-18

16-21

**Lipocalin proteins:**

36-47

120-130

**Lipocalin / cytosolic fatty-acid binding proteins:**

41-185

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**FIGURE 297**

GGGTGATTGAACTAAACCTTCGCCGCACCGAGTTTGCAGTACGGCCGTCACCCGCACCGC  
TGCCTGCTTGCGGTTGGAGAAATCAAGGCCCTACCGGGCCTCCGTAGTCACCTCTCTATA  
GTGGGCGTGGCCGAGGCCGGGGTGACCCTGCCGGAGCCTCCGCTGCCAGCGACATGTTCA  
AGGTAATTCAGAGGTCCGTGGGGCCAGCCAGCCTGAGCTTGCTCACCTTCAAAGTCTATG  
CAGCACCAAAAAAGGACTCACCTCCCAAAAATTCCGTGAAGGTTGATGAGCTTTCACCTCT  
ACTCAGTTCCCTGAGGGTCAATCGAAGTATGTGGAGGAGGCAAGGAGCCAGCTTGAAGAAA  
GCATCTCACAGCTCCGACACTATTGCGAGCCATACACAACCTGGTGTCAGGAAACGTACT  
CCCAAACCTAAGCCCAAGATGCAAAGTTTGGTTCAATGGGGGTTAGACAGCTATGACTATC  
TCCAAAATGCACCTCCTGGATTTTTTCCGAGACTTGGTGTTATTGGTTTTGCTGGCCTTA  
TTGGACTCCTTTTGGCTAGAGGTTCAAAAATAAAGAAGCTAGTGTATCCGCCTGGTTTTCA  
TGGGATTAGCTGCCTCCCTCTATTATCCACAACAAGCCATCGTGTTTGCCAGGTCAGTG  
GGGAGAGATTATATGACTGGGGTTTACGAGGATATATAGTCATAGAAGATTTGTGGAAGG  
AGAACTTTCAAAAGCCAGGAAATGTGAAGAATTACCTGGAACCTAAGTAGAAAACTCCAT  
GCTCTGCCATCTTAATCAGTTATAGGTAAACATTGGAACTCCATAGAATAAAATCAGTAT  
TTCTACAGAAAAATGGCATAGAAGTCAGTATTGAATGTATTAAATTGGCTTTCTTCTTCA  
GGAAAACTAGACCAGACCTCTGTTATCTTCTGTGAAATCATCCTACAAGCAAACTAACC  
TGGAATCCCTTCACCTAGAGATAATGTACAAGCCTTAGAACTCCTCATTCTCATGTTGCT  
ATTTATGTACCTAATTAAAACCCAAGTTTAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAA

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**FIGURE 298**

MFKVIQRSVGPASLSLLTFKVYAAPKSDSPPKNSVKVDELSTLYSVPEGQSKYVEEARSQLE  
EESISQLRHYCEPYTTWCQETYSQTKPKMQSLVQWGLDSYDYLQNAPPGFFPRLGVIGFA  
GLIGLLLARGSKIKKLVYPPGFMGLAASLYYPQQAIVFAQVSGERLYDWGLRGYIVIEDL  
WKENFQKPGNVKNSPGTK

**Important features:**

**Signal peptide:**

Amino acids 1-23

**Transmembrane domain:**

Amino acids 111-130

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

Amino acids 26-30

**Tyrosine kinase phosphorylation site:**

Amino acids 36-44

**N-myristoylation sites:**

Amino acids 124-130;144-150;189-195



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**FIGURE 299**

CCGCTGAGATGTACGAACTTCCGGTTCTCCGGGCAGCTGCCACTGCTGTAGCTTCTGCCA  
CCTGCCACGACCGGGCCTCTCCCTGGCGTTTGGTCACCTCTGCTTCATTCTCCACCGCGC  
CTATGGTCCCTCTTGGAGCCAGCGTGGCGGGCCTGGCGGGCTCCCGGGTGGTGAGAGAGCG  
GTCCGGGAACGATGAAGGCCTCGCAGTGCTGCTGCTGTCTCAGCCACCTCTTGGCTTCCG  
TCCTCCTCCTGCTGTTGCTGCCTGAACTAAGCGGGCCCCCTGGCAGTCCTGCTGCAGGCAG  
CCGAGGCCGCGCCAGGTCTTGGGCCTCCTGACCCTAGACCACGGACATTACCGCCGCTGC  
CACCGGGCCCTACCCCTGCCCAGCAGCCGGGCGGTGGTCTGGCTGAAGCTGCGGGGCCGC  
GGGGCTCCGAGGGAGGCAATGGCAGCAACCCTGTGGCCGGGCTTGAGACGGACGATCACG  
GAGGGAAGGCCGGGGAAGGCTCGGTGGGTGGCGGCCTTGCTGTGAGCCCCAACCCCTGGCG  
ACAAGCCCATGACCCAGCGGGCCCTGACCGTGTGATGGTGGTGAGCGGCGCGGTGCTGG  
TGTACTTCGTGGTCAGGACGGTCAGGATGAGAAGAAGAAACCGAAAGACTAGGAGATATG  
GAGTTTTGGACACTAACATAGAAAATATGGAATTGACACCTTTAGAACAGGATGATGAGG  
ATGATGACAACACGTTGTTTGATGCCAATCATCCTCGAAGATAAGAATGTGCCTTTTGAT  
GAAAGAACTTTATCTTTCTACAATGAAGAGTGGAATTTCTATGTTTAAGGAATAAGAAGC  
CACTATATCAATGTTGGGGGGGTATTTAAGTTACATATATTTTAACAACCTTTAATTTGC  
TGTTGCAATAAATAACCGTATCCTTTTATTATATCTTTATATGTATAGAAGTACTCTATTA  
ATGGGCTCAGAGATGTTGGGGATAAAGTATACTGTAATAATTTATCTGTTTGAAAATTAC  
TATAAAACGGTGTTTTCTGGTCCGTTTTTGTTCCTGCTTACCATATGATTGTAAATTGT  
TTTATGTATTAATCAGTTAATGCTAATTATTTTGTCTGATGTCATATGTTAAAGAGCTAT  
AAATTCCAACAACCAACTGGTGTGTAAAAATAATTTAAATTTCTTTACTGAAAGGTAT  
TTCCCATTTTTGTGGGGAAAAGAAGCCAAATTTATTACTTTGTGTTGGGGTTTTTAAAT  
ATTAAGAAATGTCTAAGTTATTGTTTGCAAAACAATAAATATGATTTTAAATTCTCTTAA  
AAAAAAA

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**FIGURE 300**

MKASQCCCCLSHLLASVLLLLLLPELSGPLAVLLQAEEAAPGLGPPDPRPRTLPPPLPPGP  
TPAQQPGRGLAEAAGPRGSEGGNGSNPVAGLETDDHGGKAGEGSVGGGLAVSPNPGDKPM  
TQRALTVMVVS GAVLVYFVVRTVRMRRNRKTRRYGVLD TN IENMELTPLEQDDEDDDN  
TLFDANHPRR

**Signal peptide:**  
amino acids 1-28

**Transmembrane domain:**  
amino acids 124-140

**N-glycosylation site:**  
amino acids 83-87

**N-myristoylation sites:**  
amino acids 69-75, 78-84, 81-87, 97-103, 103-109, 106-112,  
157-160

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**FIGURE 301**

CTCGGCTGGATTTAAGGTTGCCGCTAGCCGCTGGGAATTTAAGGGACCCACACTACCTT  
CCCGAAGTTGAAGGCAAGCGGTGATTGTTTGTAGACGGCGCTTTGTCATGGGACCTGTGC  
GGTTGGGAATATTGCTTTTCCTTTTGGCCGTGCACGAGGCTTGGGCTGGGATGTTGA  
AGGAGGAGGACGATGACACAGAACGCTTGCCCAGCAAATGCGAAGTGTGTAAGCTGCTGA  
GCACAGAGCTACAGGCGGAAGTGAAGTGCACCGGTGATCTCGAGAGGTGCTGGAGCTGG  
GGCAGGTGCTGGATACAGGCAAGAGGAAGAGACACGTGCCTTACAGCGTTTCAGAGACAA  
GGCTGGAAGAGGCTTAGAGAATTTATGTGAGCGGATCCTGGACTATAGTGTTACGCTG  
AGCGCAAGGGCTCACTGAGATATGCCAAGGGTCAGAGTCAGACCATGGCAACACTGAAAG  
GCCTAGTGCAGAAGGGGGTGAAGGTGGATCTGGGGATCCCTCTGGAGCTTTGGGATGAGC  
CCAGCGTGGAGGTCACATACCTCAAGAAGCAGTGTGAGACCATGTTGGAGGAGTTTGAAG  
ACATTGTGGGAGACTGGTACTTCCACCATCAGGAGCAGCCCCTACAAAATTTTCTCTGTG  
AAGGTCATGTGCTCCAGCTGCTGAAACTGCATGTCTACAGGAACTTGGACTGGAAAGG  
AGATCACAGATGGGGAAGAGAAAACAGAAGGGGAGGAAGAGCAGGAGGAGGAGGAGGAAG  
AGGAGGAAGAGGAAGGGGGAGACAAGATGACCAAGACAGGAAGCCACCCAACTTGACC  
GAGAAGATCTTTTGACCCTTGCCCTTGAGCCCCCAGGAGGGGAAGGGATCATGGAGAGCCC  
TCTAAAGCCTGCACTCTCCCTGCTCCACAGCTTTCAGGGTGTGTTTATGAGTGACTCCAC  
CCAAGCTTGTAGCTGTTCTCTCCCATCTAACCTCAGGCAAGATCCTGGTGAAACAGCATG  
ACATGGCTTCTGGGGTGGAGGGTGGGGGTGGAGGTCCTGCTCCTAGAGATGAACTCTATC  
CAGCCCCCTTAATTGGCAGGTGTATGTGCTGACAGTACTGAAAGCTTTCCTCTTTAACTGA  
TCCCACCCCCACCCAAAAGTCAGCAGTGGCACTGGAGCTGTGGGCTTTGGGGAAGTCACT  
TAGCTCCTTAAGGTCTGTTTTTAGACCCTTCCAAGGAAGAGGCCAGAACGGACATTCTCT  
GCGATCTATATACATTGCCTGTATCCAGGAGGCTACACACCAGCAAACCGTGAAGGAGAA  
TGGGACACTGGGTCATGGCCTGGAGTTGCTGATAATTTAGGTGGGATAGATACTTGGTCT  
ACTTAAGCTCAATGTAACCCAGAGCCCACCATATAGTTTTATAGGTGCTCAACTTTCTAT  
ATCGCTATTAACTTTTTTCTTTTTTTCTA

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**FIGURE 302**

MGPVRLGILLFLFLAVHEAWAGMLKEEDDDTERLPSKCEVCKLLSTELQAELSRTGRSRE  
VLELGQVLDTGKRKRHPYVSSETRLEEALENLCERILDYSVHAERKGSRLRYAKGQSQTM  
ATLKGLVQKGVKVDLGIPLELWDEPSVEVITYLKKQCETMLEEFEDIVGDWYFHHQEQLQ  
NFLCEGHVLPAAETACLQETWTGKEITDGEEKTEGEEEQEEEEEEEEEGGDKMTKTGSH  
PKLDREDL

**Important features of the protein:**

**Signal peptide:**

amino acids 1-21

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 106-110

**N-myristoylation site:**

amino acids 115-121

**Amidation site:**

amino acids 70-74

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**FIGURE 303**

CTCCTGCACTAGGCTCTCAGCCAGGGATGATGCGCTGCTGCCGCCGCCGCTGCTGCTGCC  
GGCAACCACCCCATGCCCTGAGGCCGTTGCTGTTGCTGCCCCCTCGTCCTTTTACCTCCCC  
TGGCAGCAGCTGCAGCGGGCCCAAACCGATGTGACACCATATAACCAGGGCTTCGCCGAGT  
GTCTCATCCGCTTGGGGGACAGCATGGGCCGCGGAGGCGAGCTGGAGACCATCTGCAGGT  
CTTGGAATGACTTCCATGCCTGTGCCTCTCAGGTCTGTGTCAGGCTGTCCGGAGGAGGCAG  
CTGCAGTGTGGGAATCACTACAGCAAGAAGCTCGCCAGGCCCCCGTCCGAATAACTTGC  
ACACTCTGTGCGGTGCCCCGGTGCATGTTCTGGGAGCGCGGCACAGGCTCCGAAACCAACC  
AGGAGACGCTGCGGGCTACAGCGCCTGCACTCCCCATGGCCCCTGCGCCCCCACTGCTGG  
CGGCTGCTCTGGCTCTGGCCTACCTCCTGAGGCCTCTGGCCTAGCTTGTTGGGTTGGGTA  
GCAGCGCCCGTACCTCCAGCCCTGCTCTGGCGGTGGTTGTCCAGGCTCTGCAGAGCGCAG  
CAGGGCTTTTCATTAAAGGTATTTATATTTGTA

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**FIGURE 304**

MMRCCRRRCCCRQPPHALRPLLLLPLVLLPPLAAAAAGPNRCDTIYQGFAECLIRLGDSM  
GRGGELETICRSWNDFHACASQVLSGCPPEEAAVWESLQQEARQAPRPNNLHTLCGAPVH  
VRERGTGSETNQETLRATAPALPMAPAPPLLAALALAYLLRPLA

**Signal peptide:**

Amino acids 1-35

**Transmembrane domain:**

Amino acids 141-157

**N-myristoylation site:**

Amino acids 127-133

**Prokaryotic membrane lipoprotein lipid attachment site:**

Amino acids 77-88

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**FIGURE 305**

AAGTACTTGTGTCCGGGTGGTGGACTGGATTAGCTGCGGAGCCCTGGAAGCTGCCTGTCC  
TTCTCCCTGTGCTTAACCAGAGGTGCCCATGGGTGGACAATGAGGCTGGTCACAGCAGC  
ACTGTTACTGGGTCTCATGATGGTGGTCACTGGAGACGAGGATGAGAACAGCCCGTGTGC  
CCATGAGGCCCTCTTGGACGAGGACACCCTCTTTTGCCAGGGCCTTGAAGTTTTCTACCC  
AGAGTTGGGGAACATTGGCTGCAAGGTTGTTCCCTGATTGTAACAACCTACAGACAGAAGAT  
CACCTCCTGGATGGAGCCGATAGTCAAGTTCCCGGGGGCCGTGGACGGCGCAACCTATAT  
CCTGGTGATGGTGGATCCAGATGCCCCCTAGCAGAGCAGAACCCAGACAGAGATTCTGGAG  
ACATTGGCTGGTAACAGATATCAAGGGCGCCGACCTGAAGAAAGGGAAGATTCAAGGGCCA  
GGAGTTATCAGCCTACCAGGCTCCCTCCCCACCGGCACACAGTGGCTTCCATCGCTACCA  
GTTCTTTGTCTATCTTCAGGAAGGAAAAGTCATCTCTCTCCTTCCCAAGGAAAACAAAAC  
TCGAGGCTCTTGGAAAATGGACAGATTTCTGAACCGCTTCCACCTGGGCGAACCTGAAGC  
AAGCACCCAGTTCATGACCCAGAACTACCAGGACTCACCAACCCTCCAGGCTCCAGAGG  
AAGGGCCAGCGAGCCCAAGCACAAAACCAGGCAGAGATAGCTGCCTGCTAGATAGCCGGC  
TTTGCCATCCGGGCATGTGGCCCACTGCTCACCACCGACGATGTGGGTATGGAACCCCC  
TCTGGATACAGAACCCTTCTTTTCCAAATTAAAAAAAAAAATCATCAA

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**FIGURE 306**

MGWTMRLVTAALLLGLMMVVTGDEDENSPCAHEALLDEDTLFCQGLEVFYPELGNI GCKV  
VPDCNNYRQKITSWMEPIVKFPGAVDGATYILVMVDPDAPSRAEPRQRFWRHWLVTDIKG  
ADLKKGKIQGQELSAYQAPSPPAHSGFHR YQFFVYLQEGKVISLLPKENKTRGSWKMDRF  
LNR FHLGEPEASTQFMTQNYQDSPTLQAPRGRASEPKHKTRQR

**Important features of the protein:**

**Signal peptide:**

amino acids 1-22

**N-glycosylation site:**

amino acids 169-173

**Tyrosine kinase phosphorylation site:**

amino acids 59-68

**N-myristoylation sites:**

amino acids 54-60, 83-89, 130-136

**Phosphatidylethanolamine signature:**

amino acids 113-157



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**FIGURE 307**

AAGGAGCAGCCCGCAAGCACCAAGTGAGAGGCATGAAGTTACAGTGTGTTTCCCTTTGGC  
TCCTGGGTACAATACTGATATTGTGCTCAGTAGACAACCACGGTCTCAGGAGATGTCTGA  
TTTCCACAGACATGCACCATATAGAAGAGAGTTTCCAAGAAATCAAAAGAGCCATCCAAG  
CTAAGGACACCTTCCCAAATGTCACTATCCTGTCCACATTGGGAGACTCTGCAGATCATTA  
AGCCCTTAGATGTGTGCTGCGTGACCAAGAACCTCCTGGCGTTCTACGTGGACAGGGTGT  
TCAAGGATCATCAGGAGCCAAACCCAAAATCTTGAGAAAAATCAGCAGCATTGCCAACT  
CTTTCCTCTACATGCAGAAAACCTCTGCGGCAATGTCAGGAACAGAGGCAGTGTCACTGCA  
GGCAGGAAGCCACCAATGCCACCAGAGTCATCCATGACAACCTATGATCAGCTGGAGGTCC  
ACGCTGCTGCCATTAAATCCCTGGGAGAGCTCGACGTCTTCTAGCCTGGATTAATAAGA  
ATCATGAAGTAATGTTCTCAGCTTGATGACAAGGAACCTGTATAGTGATCCAGGGATGAA  
CACCCCCTGTGCGGTTTACTGTGGGAGACAGCCACCTTGAAGGGGAAGGAGATGGGGAA  
GGCCCCCTTGACAGCTGAAAGTCCCACTGGCTGGCCTCAGGCTGTCTTATTCCGCTTGAAAA  
TAGGCAAAAAGTCTACTGTGGTATTTGTAATAAACTCTATCTGCTGAAAGGGCCTGCAGG  
CCATCCTGGGAGTAAAGGGCTGCCTTCCCATCTAATTTATTGTAAAGTCATATAGTCCAT  
GTCTGTGATGTGAGCCAAGTGATATCCTGTAGTACACATTGTACTGAGTGGTTTTTCTGA  
ATAAATTCATATTTTACCTATGA

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**FIGURE 308**

MKLQCVSLWLLGTILILCSVDNHGLRRCLISTDMHHIEESFQEIKRAIQAKDTFPNVTIL  
STLETLQIIKPLDVCCVTKNLLAFYVDRVFKDHQEPNPKILRKISSIANSFLYMQKTLRQ  
CQEQRQCHCRQEATNATRVIHNDYDQLEVHAAAIKSLGELDVFLAWINKNHEVMFSA

**Signal sequence:**  
amino acids 1-18

**N-glycosylation sites:**  
amino acids 56-60, 135-139

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 102-106

**N-myristoylation site:**  
amino acids 24-30

**Actinin-type actin-binding domain signature 1:**  
amino acids 159-169

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**FIGURE 309**

GTCGACCCACGCGTCCGAAGCTGCTGGAGCCACGATTTCAGTCCCCTGGACTGTAGATAAA  
GACCCTTTCCTTGCCAGGTGCTGAGACAACCACACTATGAGAGGCACTCCAGGAGACGCTG  
ATGGTGGAGGAAGGGCCGCTCTATCAATCAATCACTGTTGCTGTTATCACATGCAAGTATC  
CAGAGGCTCTTGAGCAAGGCAGAGGGGATCCCATTTATTTGGGAATCCAGAATCCAGAAA  
TGTGTTTGTATTGTGAGAAGGTTGGAGAACAGCCACATTGCAGCTAAAAGAGCAGAAGA  
TCATGGATCTGTATGGCCAACCCGAGCCCGTGAAACCCTTCCTTTTCTACCGTGCCAAGA  
CTGGTAGGACCTCCACCCTTGAGTCTGTGGCCTTCCCGGACTGGTTTCATTGCCTCCTCCA  
AGAGAGACCAGCCCATCATTCTGACTTCAGAACTTGGGAAGTCATACAACACTGCCTTTG  
AATTAAATATAAATGACTGAACTCAGCCTAGAGGTGGCAGCTTGGTCTTTGCTTTAAAGT  
TTCTGGTTCCCAATGTGTTTTTCGTCTACATTTTCTTAGTGTCAATTTTCACGCTGGTGCTG  
AGACAGGAGCAAGGCTGCTGTTATCATCTCATTTTATAATGAAGAAGAAGCAATTACTTC  
ATAGCAACTGAAGAACAGGATGTGGCCTCAGAAGCAGGAGAGCTGGGTGGTATAAGGCTG  
TCCTCTCAAGCTGGTGCTGTGTAGGCCACAAGGCATCTGCATGAGTGACTTTAAGACTCA  
AAGACCAAACACTGAGCTTTCTTCTAGGGGTGGGTATGAAGATGCTTCAGAGCTCATGCG  
CGTTACCCACGATGGCATGACTAGCACAGAGCTGATCTCTGTTTTCTGTTTTGCTTTATTC  
CCTCTTGGGATGATATCATCCAGTCTTTATATGTTGCCAATATACCTCATTGTGTGTAAT  
AGAACCTTCTTAGCATTAAGACCTTGTAACAAAAATAATTCTTGGGGTGGGTATGAAGA  
TGCTTCAGAGCTCATGCGGTTACCCACGATGGCATGACTAGCACAGAGCTGATCTCTGT  
TTCTGTTTTGCTTTATTCCCTCTTGGGATGATATCATCCAGTCTTTATATGTTGCCAATA  
TACCTCATTGTGTGTAATAGAACCTTCTTAGCATTAAGACCTTGTAACAAAAATAATTC  
TTGTGTTAAGTTAAATCATTTTTGTCCTAATTGTAATGTGTAATCTTAAAGTTAAATAAA  
CTTTGTGTATTTATATAATAATAAAGCTAAAACTGATATAAAATAAAGAAAGAGTAAACTG

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## FIGURE 310

MRGTPGDADGGGRAVYQSITVAVITCKYPEALEQGRGDPIYLGIONPEMCLYCEKVGEQP  
TLQLKEQKIMDLYGQPEPVKPFLFYRAKTGRTSTLESVAFPDWFIASSKRDQPIILTSEL  
GKSYNTAFELNIND

**Signal sequence:**  
amino acids 1-17

**N-myristoylation site:**  
amino acids 10-16

**Cell attachment sequence:**  
amino acids 36-39

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**FIGURE 311**

GCGAGGCTGCACCAGCGCCTGGCACCATGAGGACGCCTGGGCCTCTGCCCCGTGCTGCTGC  
TGCTCCTGGCGGGAGCCCCGCGCGCGGCCACTCCCCGACCTGCTACTCCCGCATGC  
GGGCCCTGAGCCAGGAGATCACCCGCGACTTCAACCTCCTGCAGGTCTCGGAGCCCTCGG  
AGCCATGTGTGAGATACCTGCCCAGGCTGTACCTGGACATACACAATTACTGTGTGCTGG  
ACAAGCTGCGGGACTTTGTGGCCTCGCCCCCGTGTGGAAAGTGGCCCAGGTAGATTCTT  
TGAAGGACAAAGCACGGAAGCTGTACACCATCATGAACTCGTTCTGCAGGAGAGATTTGG  
TATTCCTGTTGGATGACTGCAATGCCTTGGAATACCCAATCCCAGTGACTACGGTCCTGC  
CAGATCGTCAGCGCTTAAGGGAAGTGAAGACCAGAGAAAGAACCCAAGAGAACTAAAGTTAT  
GTCAGCTACCCAGACTTAATGGGCCAGAGCCATGACCCTCACAGGTCTTGTGTTAGTTGT  
ATCTGAAACTGTTATGTATCTCTACCTTCTGGAAAACAGGGCTGGTATTCCTACCCAG  
GAACCTCCTTTGAGCATAGAGTTAGCAACCATGCTTCTCATTCCCTTGACTCATGTCTTG  
CCAGGATGGTTAGATACACAGCATGTTGATTGGTCACTAAAAAGAAGAAAAGGACTAAC  
AAGCTTCACTTTTATGAACAACTATTTTGAGAACATGCACAATAGTATGTTTTTATTACT  
GGTTTAATGGAGTAATGGTACTTTTATTCTTTCTTGATAGAAACCTGCTTACATTTAACC  
AAGCTTCTATTATGCCTTTTCTAACACAGACTTTCTTCACTGTCTTTCAATTTAAAAAGA  
AATTAATGCTCTTAAGATATATATTTTACGTAGTGCTGACAGGACCCACTCTTTCATTGA  
AAGGTGATGAAAATCAAATAAAGAATCTCTTCACATGGA

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## FIGURE 312

MRTPGPLPVLLLLLAGAPAARPTPPTCYSRMRALSQEITRDFNLLQVSEPSEPCVRYLPR  
LYLDIHNYCVLDKLRDFVASPPCWKVAQVDSLKDKARKLYTIMNSFCRRDLVFLDDCNA  
LEYPIPVTTVLPRDR

**Important features of the protein:**

**Signal peptide:**

amino acids 1-19

**Tyrosine kinase phosphorylation site:**

amino acids 60-69

**N-myristoylation site:**

amino acids 16-22

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**FIGURE 313**

GAGCGACGCTGTCTCTAGTCGCTGATCCCAAATGCACCGGCTCATCTTTGTCTACACTCT  
AATCTGCGCAAACCTTTTGCAGCTGTCGGGACACTTCTGCAACCCCGCAGAGCGCATCCAT  
CAAAGCTTTGCGCAACGCCAACCTCAGGCGAGATGACTTGTACCGAAGAGATGAGACCAT  
CCAGGTGAAAGGAAACGGCTACGTGCAGAGTCCTAGATTCCCGAACAGCTACCCAGGAA  
CCTGCTCCTGACATGGCGGCTTCACTCTCAGGAGAATACACGGATACAGCTAGTGTGTTGA  
CAATCAGTTTGGATTAGAGGAAGCAGAAAATGATATCTGTAGGTATGATTTTGTGGAAGT  
TGAAGATATATCCGAAACCAGTACCATTATTAGAGGACGATGGTGTGGACACAAGGAAGT  
TCCTCCAAGGATAAAATCAAGAACGAACCAAATTAATAATCACATTCAAGTCCGATGACTA  
CTTTGTGGCTAAACCTGGATTCAAGATTTATTATTCTTTGCTGGAAGATTCCAACCCGC  
AGCAGCTTCAGAGACCAACTGGGAATCTGTACAAGCTCTATTTCAAGGGGTATCCTATAA  
CTCTCCATCAGTAACGGATCCCCTCTGATTGCGGATGCTCTGGACAAAAAATTGCAGA  
ATTTGATACAGTGGAAGATCTGCTCAAGTACTTCAATCCAGAGTCATGGCAAGAAGATCT  
TGAGAATATGTATCTGGACACCCCTCGGTATCGAGGCAGGTCATACCATGACCGGAAGTC  
AAAAGTTGACCTGGATAGGCTCAATGATGATGCCAAGCGTTACAGTTGCACTCCCAGGAA  
TTACTCGGTCAATATAAGAGAAGAGCTGAAGTTGGCCAATGTGGTCTTCTTTCCACGTTG  
CCTCCTCGTGCAGCGCTGTGGAGGAAATTGTGGCTGTGGAAGTGTCAACTGGAGGTCCTG  
CACATGCAATTCAGGGAAAACCGTGAAAAAGTATCATGAGGTATTACAGTTTGAGCCTGG  
CCACATCAAGAGGAGGGGTAGAGCTAAGACCATGGCTCTAGTTGACATCCAGTTGGATCA  
CCATGAACGATGCGATTGTATCTGCAGCTCAAGACCACCTCGATTAAGAGAATGTGCACAT  
CCTTACATTAAGCCTGAGAGAA

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**FIGURE 314**

MHRLIFVYTLICANFCSCRDTSATPQSASIKALRNANLRRDDLYRRDETIQVKGNGYVQS  
PRFPNSYPRNLLLTWRLHSQENTRIQLVFDNQFGLLEEAENDICRYDFVEVEDISETSTII  
RGRWCGHKEVPPRIKSRTNQIKITFKSDDYFVAKPGFKIYYSLLEDFQPAAASETNWESV  
TSSISGVSYNPSVTDPTLIADALDKKIAEFDTVEDLLKYFNPESWQEDLENMYLDTPRY  
RGRSYHDRKSKVDLRLNDDAKRYSCTPRNYSVNIREELKLANVFFPRCLLVQRCGGNC  
GCGTVNWRSCTCNSGKTVKKYHEVLQFEPGHIKRRGRAKTMALVDIQLDHHERCDCICSS  
RPPR

**Signal peptide:**

amino acids 1-18

**N-glycosylation site:**

amino acids 270-274

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 262-266

**Tyrosine kinase phosphorylation site:**

amino acids 256-265

**N-myristoylation sites:**

amino acids 94-100, 186-192, 297-303, 298-304

**TonB-dependent receptor proteins signature 1:**

amino acids 1-56



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**FIGURE 315**

CGGCTCGAGGCTCCCGCCAGGAGAAAGGAACATTCTGAGGGGAGTCTACACCCTGTGGAG  
CTCAAGATGGTCTCTGAGTGGGGCGCTGTGCTTCCGAATGAAGGACTCGGCATTGAAGGTG  
CTTTATCTGCATAATAACCAGCTTCTAGCTGGAGGGCTGCATGCAGGGAAGGTCATTAAA  
GGTGAAGAGATCAGCGTGGTCCCAATCGGTGGCTGGATGCCAGCCTGTCCCCCGTCATC  
CTGGGTGTCCAGGGTGAAGCCAGTGCCTGTCTGTGGGGTGGGGCAGGAGCCGACTCTA  
ACACTAGAGCCAGTGAACATCATGGAGCTCTATCTTGGTGCCAAGGAATCCAAGAGCTTC  
ACCTTCTACCGGCGGGACATGGGGCTCACCTCCAGCTTCGAGTCGGCTGCCTACCCGGGC  
TGGTTCCTGTGCACGGTGCCTGAAGCCGATCAGCCTGTCTCAGACTCACCCAGCTTCCCGAG  
AATGGTGGCTGGAATGCCCCCATCACAGACTTCTACTTCCAGCAGTGTGACTAGGGCAAC  
GTGCCCCCAGAACTCCCTGGGCAGAGCCAGCTCGGGTGAGGGGTGAGTGGAGGAGACCC  
ATGGCGGACAATCACTCTCTCTGCTCTCAGGACCCCCACGTCTGACTTAGTGGGCACCTG  
ACCACTTTGTCTTCTGGTTCCAGTTTGGATAAAATTCTGAGATTTGGAGCTCAGTCCACG  
GTCCTCCCCCACTGGATGGTGTCTACTGTCTGTGGAACCTTGTA AAAACCATGTGGGGTAAA  
CTGGGAATAACATGAAAAGATTTCTGTGGGGGTGGGGTGGGGGAGTGGTGGGAATCATTC  
CTGCTTAATGGTAACTGACAAGTGTTACCCTGAGCCCCGCAGGCCAACCCATCCCCAGTT  
GAGCCTTATAGGGTCACTAGCTCTCCACATGAAGTCCTGTCACTCACCCTGTGCAGGAG  
AGGGAGGTGGTCATAGAGTCAGGGATCTATGGCCCTTGGCCCAGCCCCACCCCTTCCCT  
TTAATCCTGCCACTGTCTATATGCTACCTTTCCTATCTCTTCCCTCATCATCTTGTGTGG  
GCATGAGGAGGTGGTGTATGTCTAGAAGAAATGGCTCGAGCTCAGAAGATAAAAGATAAGTA  
GGGTATGCTGATCCTCTTTTAAAAACCCAAGATACAATCAAAATCCAGATGCTGGTCTC  
TATTCCTCATGAAAAAGTGCTCATGACATATTGAGAAGACCTACTTACAAAGTGGCATATA  
TTGCAATTTATTTTAATTAAAAGATACCTATTTATATATTTCTTTATAGAAAAAAGTCTG  
GAAGAGTTTACTTCAATTGTAGCAATGTCTAGGGTGGTGGCAGTATAGGTGATTTTCTTT  
TAATTCGTGTTAATTTATCTGTATTTCTTAATTTTCTACAATGAAGATGAATTCCTGTGA  
TAAAAATAAGAAAAGAAATTAATCTTGAGGTAAGCAGAGCAGACATCATCTCTGATTGTC  
CTCAGCCTCCACTTCCCCAGAGTAAATTCAAATTGAATCGAGCTCTGCTGCTCTGGTTGG  
TTGTAGTAGTGATCAGGAAACAGATCTCAGCAAAGCCACTGAGGAGGAGGCTGTGCTGAG  
TTTGTGTGGCTGGAATCTCTGGGTAAGGAACCTTAAAGAACAAAAATCATCTGGTAATTCT  
TTCCTAGAAGGATCACAGCCCCCTGGGATTCCAAGGCATTGGATCCAGTCTCTAAGAAGGC  
TGCTGTACTGGTTGAATTGTGTCCCCCTCAAATTCACATCCTTCTTGGAATCTCAGTCTG  
TGAGTTTATTTGGAGATAAGGTCTCTGCAGATGTAGTTAGTTAAGACAAGGTCATGCTGG  
ATGAAGGTAGACCTAAATTCAATATGACTGGTTTCTTGTATGAAAAGGAGAGGACACAG  
AGACAGAGGAGACGCGGGGAAGACTATGTAAAGATGAAGGCAGAGATCGGAGTTTTCAG  
CCACAAGCTAAGAAACACCAAGGATTGTGGCAACCATCAGAAGCTTGGAAGAGGCAAGA  
AGAATTCTTCCCTAGAGGCTTTAGAGGGATAACGGCTCTGCTGAAACCTTAATCTCAGAC  
TTCCAGCCTCCTGAACGAAGAAAGATAAAATTTCCGGCTGTTTTAAAGCCACCAAGGATAAT  
TGGTTACAGCAGCTCTAGGAAACTAATACAGCTGCTAAAATGATCCCTGTCTCCTCGTGT  
TTACATTCTGTGTGTGTCCCCCTCCACAATGTACCAAAGTTGTCTTTGTGACCAATAGAA  
TATGGCAGAAGTGATGGCATGCCACTTCCAAGATTAGGTTATAAAAGACACTGCAGCTTC  
TACTTGAGCCCTCTCTCTCTGCCACCCACCGCCCCCAATCTATCTTGGCTCACTCGCTCT  
GGGGGAAGCTAGCTGCCATGCTATGAGCAGGCCTATAAAGAGACTTACGTGGTAAAAAAT  
GAAGTCTCCTGCCACAGCCACATTAGTGAACCTAGAAGCAGAGACTCTGTGAGATAATC  
GATGTTTGTGTTGTTTAAAGTTGCTCAGTTTTGGTCTAAGTTGTTATGCAGCAATAGATAAA  
TAATATGCAGAGAAAGAG

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**FIGURE 316**

MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHAGKVIKGEEISVVPNRWLDASLSPVILG  
VQGGSQCLSCGVGQEPTLTLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWF  
LCTVPEADQPVRILTQLPENGGWNAPIITDFYFQQCD

**N-myristoylation sites:**

amino acids 29-34, 30-35, 60-65, 63-68, 73-78, 91-96, 106-111

**Interleukin-1 signature:**

amino acids 111-131

**Interleukin-1 proteins:**

amino acids 8-29, 83-120, 95-134, 64-103

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**FIGURE 317**

ATGGAACTTGGACTTGGAGGCCTCTCCACGCTGTCCCACTGCCCCTGGCCTAGGCGGCAG  
CCTGCCCTGTGGCCCACCCTGGCCGCTCTGGCTCTGCTGAGCAGCGTCGCAGAGGCCTCC  
CTGGGCTCCGCGCCCCGCAGCCCTGCCCCCGCGAAGGCCCCCGCCTGTCCTGGCGTCC  
CCCGCCGGCCACCTGCCGGGGGGACGCACGGCCCGCTGGTGCAAGAGAGCCCGGCGG  
CCGCGCCCGCAGCCTTCTCGGCCCCGCGCCCCCGCCGCTGCACCCCCATCTGCTCTTCCC  
CGCGGGGGCCGCGCGGCGCGGGCTGGGGGCCCGGGCAGCCGCGCTCGGGCAGCGGGGGCG  
CGGGGCTGCCGCTGCGCTCGCAGCTGGTGCCGGTGCGCGGCTCGGCCTGGGCCACCGC  
TCCGACGAGCTGGTGCGTTTCCGCTTCTGCAGCGGCTCCTGCCGCCGCGCGCGCTCTCCA  
CACGACCTCAGCCTGGCCAGCCTACTGGGCGCCGGGGCCCTGCGACCGCCCCCGGGCTCC  
CGGCCCCTCAGCCAGCCCTGCTGCCGACCCACGCGCTACGAAGCGGTCTCCTTCATGGAC  
GTCAACAGCACCTGGAGAACCGTGGACCGCCTCTCCGCCACCGCCTGCGGCTGCCTGGGC  
TGA

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**FIGURE 318**

MELGLGGLSTLSHCPWPRRQPALWPTLAALALLSSVAEASLGSA PRSPAPREGPPPVLAS  
PAGHLPGGRTARWCSGRARRPPPQPSRPAPPPPAPPSALPRGGRAARAGGPGRARAAGA  
RGCRLRSQ LVPVRALGLGHRSDLVRFRCGSGSCRRARSPHDLSLASLLGAGALRPPPGS  
RPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATA CGCLG

**signal sequence:**

Amino acids 1-39

**N-glycosylation site:**

Amino acids 202-206

**N-myristoylation sites:**

Amino acids 6-12;67-73;102-108;109-115;119-125

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**FIGURE 319**

GTTGCTATGTTGCCCAGGCTGGTCTTGAAGTGCCTTGACCTCCTAAAGTGTTGGAACCAC  
AGACGTGAGCCACTCCACCCAGCCTAAAACTTCATCTTCTTTGGATGAGATGAACACTTT  
TAACAAGAGAACAGGACTCTATATAAATCGCTGTGGGCTCACCACCTCTAAGGAGGAGCA  
CTGACTGAAGACAGAAAAATTGATGAACTGAAGAAGACATGGTCCATTATGCCTTACAAA  
CTTACACAGTGCTTTGGGAATTCCAAAGTACTCAGTGGAGAGAGGTGTTTCAGGAGCCGT  
AGAGCCAGATCGTCATCATGTCTGCATTGTGGCTGCTGCTGGGCCTCCTTGCCCTGATGG  
ACTTGTCTGAAAGCAGCAACTGGGGATGCTATGGAAACATCCAAAGCCTGGACACCCCTG  
GAGCATCTTGTGGGATTGGAAGACGTCACGGCCTGAACTACTGTGGAGTTCGTGCTTCTG  
AAAGGCTGGCTGAAATAGACATGCCATACCTCCTGAAATATCAACCCATGATGCAAACCA  
TTGGCCAAAAGTACTGCATGGATCCTGCCGTGATCGCTGGTGTCTTGTCCAGGAAGTCTC  
CCGGTGACAAAATTCTGGTCAACATGGGCGATAGGACTAGCATGGTGCAGGACCCTGGCT  
CTCAAGCTCCACATCCTGGATTAGTGAGTCTCAGGTTTCCCAGACAACTGAAGTTCTGA  
CTACTAGAATCAAAGAAATCCAGAGGAGGTTTCCAACCTGGACCCCTGACCAGTACCTGA  
GAGGTGGACTCTGTGCCTACAGTGGGGGTGCTGGCTATGTCCGAAGCAGCCAGGACCTGA  
GCTGTGACTTCTGCAATGATGTCTTGCACGAGCCAAGTACCTCAAGAGACATGGCTTCT  
AACATCTCAGATGAAACCCAAGACCATGATCACATATGCAGCCTCAAATGTTACACAGAT  
AAAAGTAGCCAAGGGCACCTGTAACTGGGAATCTGAGTTTGACCTAAAAGTCATTAAAAT  
AACATGAATCCCATTAATAAAAAAAAAAAAAA

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**FIGURE 320**

MSALWLLLGLLALMDLSESSNWGCYGNIQSLDTPGASCGIGRRHGLNYCGVRASERLAEI  
DMPYLLKYQPMQTIGQKYCMDPAVIAGVLSRKSPGDKILVNMGDRTSMVQDPGSQAPTS  
WISESQVSQTTEVLTTRIKEIQRRFPTWTPDQYLRGGLCAYSGGAGYVRSSQDLSCDFCN  
DVLARAKYLKRHGF

**Important features of the protein:****Signal peptide:**

amino acids 1-19

**N-myristoylation sites:**

amino acids 23-29, 26-32, 35-41, 45-51, 50-56, 76-82, 156-162

**Amidation site:**

amino acids 40-44

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**FIGURE 321**

GCCTTATAAAGTAGCCTCTGCATCTGCCTGCCTCGGGCAGAGGAGGGCTACCCTGGGGCT  
GAGAGTTCACCTGTCTCAGGAACCACCTGAGCCCACAGATCCTGTGGGCAGCGGCCAGGG  
CAGCCATGGCTTGGGCAAGTAGGCTGGGCCTGCTGCTGGCACTGCTGCTGCCCCGTGGTCTG  
GTGCCTCCACGCCAGGCACCGTGGTCCGACTCAACAAGGCAGCATTGAGCTACGTGTCTG  
AAATTGGGAAAGCCCCCTCTCCAGCGGGCCCTGCAGGTCACCTGTCCCTCATTTCTGGACT  
GGAGTGGAGAGGCGCTTCAGCCCACCAGGATCCGGATTCTGAATGTCCATGTGCCCCGCC  
TCCACCTGAAATTCATTGCTGGTTTCGGAGTGCGCCTGCTGGCAGCAGCTAATTTTACTT  
TCAAGGTCTTTCGCGCCCCAGAGCCCCCTGGAGCTGACGCTGCCTGTGGAACCTGCTGGCTG  
ACACCCGCGTGACCCAGAGCTCCATCAGGACCCCCTGTGGTCAGCATCTCTGCCTGCTCTT  
TATTCTCGGGCCACGCCAACGAGTTTGATGGCAGTAACAGCACCTCCACGCGCTGCTGG  
TCCTGGTGCAGAAGCACATTAAAGCTGTCTTGAGTAACAAGCTGTGCCTGAGCATCTCCA  
ACCTGGTGCAGGGTGTCAATGTCCACCTGGGCACCTTAATTGGCCTCAACCCCGTGGGTCT  
CTGAGTCCCAGATCCGCTATTCCATGGTCAGTGTGCCCCTGTCACCAGTGACTACATTT  
CCCTGGAAGTCAATGCTGTTCTCTTCTGCTGGGCAACCCCATCATCCTGCCCACGGATG  
CCACCCCTTTTGTGTTGCCAAGGCATGTGGGTACCGAGGGCTCCATGGCCACCGTGGGCC  
TCTCCAGCAGCTGTTTGACTCTGCGCTCCTGCTGCTGCAGAAGGCCGGTGCCCTCAACC  
TGGACATCACAGGGCAGCTGAGGTCGGATGACAACCTGCTGAACACCTCTGCTCTGGGCC  
GGCTCATCCCGGAGGTGGCCCGCCAGTTTCCCGAGCCCATGCCTGTGGTGCTCAAGGTGC  
GGCTGGGTGCCACACCTGTGGCCATGCTCCACACAAACAACGCCACCCCTGCGGCTGCAGC  
CCTTCGTGGAGGTCTGGCCACAGCCTCCAACTCGGCTTTCCAGTCCCTCTTCTCCCTGG  
ATGTGGTAGTGAACCTTGAGACTCCAGCTCTCTGTGTCCAAGGTGAAGCTTCAGGGGACCA  
CGTCTGTGCTGGGGGATGTCCAGCTCACGGTGGCCTCCTCCAACGTGGGCTTCATTGATA  
CAGATCAGGTGCGCACACTGATGGGCACCGTTTTTTGAGAAGCCCCCTGCTGGACCATCTCA  
ATGCTCTCTTGGCCATGGGAATTGCCCTCCCTGGTGTGGTCAACCTCCACTATGTTGCC  
CTGAGATCTTTGTCTATGAGGGCTACGTGGTGATATCCAGTGGACTCTTCTACCAGAGCT  
GAGGCAAGACCACTGGGAGGCCTGAGAGTGGGCCAGCTCGCTGCTCAGGCGAATTTCTCA  
TTTCAAGCCACTGGGGAACTGAGGCAAAACCATACTTAGTCATCACCAACAAGCTGGAC  
TGCTTAGCTGGGCTGTTTTATCTTCCCTGAGTGCCTGGGTCTCCCTCCCTCACTTCTGCC  
CTTTCCCTTCCCTCCTCCTCTTCTCCTCCCTCTTCCCTCATCTCCCCCTCCTTCCCTCTGC  
CCCACCCAGGGGGGAGCAGACTGCTCCTCCAGGCTGTATAGACCTGCCCTCTTGCATTA  
AACAACCTCTCTTGAGCTGC

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**FIGURE 322**

MAWASRLGLLLALLLPVVGASTPGTVVRLNKAALSYVSEIGKAPLQRALQVTVPHFLDWS  
GEALQPTRIRILNVHVPRLHLKFIAGFGVRLLAANFTFKVFRAPPELELTLPVELLADT  
RVTQSSIRTPVVSISACSLFSGHANEFDGSNSTSHALLVLVQKHIKAVLSNKLCLSISNL  
VQGVNVHLGTLIGLNPVGPESQIRYSMVSVPTVTS DYISLEVNAVLFLLGNPIILPTDAT  
PFVLPRHVGTEGSMATVGLSQQLFDSALLLLQKAGALNLDITGQLRSDDNLLNTSALGRL  
IPEVARQFPEPMPVVLKVR LGATPVAMLHTNNATLRLQPFVEVLATASNSAFQSLFSLDV  
VVNLRLQLSVSKVKLQGTTSVLGDVQLTVASSNVGFIDTDQVRTLMGTVF EKPLLDHLNA  
LLAMGIALPGVVNLHYVAPEIFVYEGYVVISSGLFYQS

**Important features of the protein:****Signal peptide:**

Amino acids 1-20

**Transmembrane domain:**

Amino acids 217-236

**N-glycosylation sites:**

Amino acids 96-100;151-155;293-297;332-336

**N-myristoylation sites:**

Amino acids 8-14;149-155;189-195;249-255;252-258;283-289

**LBP / BPI / CETP family proteins:**

Amino acids 22-50; 251-287



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**FIGURE 323**

TTGAAAATCTACTCTATCAGCTGCTGTGGTTGCCACCATTCTCAGGACCCTCGCCATGAA  
AGCCCTTATGCTGCTCACCCTGTCTGTTCTGCTCTGCTGGGTCTCAGCTGACATTGCTG  
TCACTCCTGCTACAAGGTCCCTGTGCTGGGCTGTGTGGACCGGCAGTCCTGCCGCCTGGA  
GCCAGGACAGCAATGCCTGACAACACATGCATACCTTGGTAAGATGTGGGTTTTCTCCAA  
TCTGCGCTGTGGCACACCAGAAGAGCCCTGTCAGGAGGCCTTCAACCAAACCAACCGCAA  
GCTGGGTCTGACATATAACACCACCTGCTGCAACAAGGACAACCTGCAACAGCGCAGGACC  
CCGGCCCCACTCCAGCCCTGGGCCTTGTCTTCCTTACCTCCTTGGCTGGCCTTGGCCTCTG  
GCTGCTGCACTGAGACTCATTCCATTGGCTGCCCCCTCCTCCCACCTGCCTTGGCCTGAGC  
CTCTCTCCCTGTGTCTCTGTATCCCCTGGCTTTACAGAATCGTCTCTCCCTAGCTCCCAT  
TTCTTTAATTAAACACTGTTCCGAGTGGTCTCCTCATCCATCCTTCCCACCTCACACCCT  
TCACTCTCCTTTTTCTGGGTCCCTTCCCCTTCCCTTCCAGGACCTCCATTGGCTCCTAGA  
AGGGCTCCCCACTTTGCTTCCTATACTCTGCTGTCCCCTACTTGAGGAGGGATTGGGATC  
TGGGCCTGAAATGGGGCTTCTGTGTTGTCCCCAGTGAAGGCTCCCACAAGGACCTGATGA  
CCTCACTGTACAGAGCTGACTCCCCAAACCCAGGCTCCCATATGTACCCCATCCCCCATA  
CTCACCTCTTCCATTTTGAGTAATAAATGTCTGAGTCTGGAAAAAAAAAAAAAAAAAAAA

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**FIGURE 324**

MKALMLLTLSVLLCWVSADIRCHSCYKVPVLGCVDRQSCRLEPGQQCLTTHAYLGKMWVF  
SNLRCGTPEEPCQEAFNQTNRKLGTYNTTCCNKDNCNSAGPRPTPALGLVFLTSLAGLG  
LWLLH

**Important features of the protein:**

**Signal peptide:**

amino acids 1-18

**N-glycosylation sites:**

amino acids 77-81, 88-92

**N-myristoylation site:**

amino acids 84-90

**Ly-6 / u-PAR domain protein signature:**

amino acids 85-98

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**FIGURE 325**

ACGGGCCGCGACGGCAGTGACGTAGGGTTGGCGCACGGATCCGTTGCGGCTGCAGCTCTG  
CAGTCGGGCCGTTTCCTTCGCCGCCGCCAGGGGTAGCGGTGTAGCTGCGCAGCGTCGCGCG  
CGCTACCGCACCCAGGTTTCGGCCCCGTAGGCGTCTGGCAGCCCGGCGCCATCTTCATCGAG  
CGCCATGGCCCGCAGCCTGCGGGCCGGGAGCGGCCGGGTACTGCTTGCTCCTCGGCTTGCA  
TTTGTTTCTGCTGACCGCGGGCCCTGCCCTGGGCTGGAACGACCCTGACAGAATGTTGCT  
GCGGGATGTAAAAGCTCTTACCCTCCACTATGACCGCTATACCACCTCCCGCAGGCTGGA  
TCCCATCCACAGTTGAAATGTGTTGGAGGCACAGCTGGTTGTGATTCTTATACCCCAA  
AGTCATACAGTGTCAGAACAAAGGCTGGGATGGGTATGATGTACAGTGGGAATGTAAGAC  
GGACTTAGATATTGCATACAAATTTGGAAAACTGTGGTGAGCTGTGAAGGCTATGAGTC  
CTCTGAAGACCAGTATGTACTAAGAGGTTCTTGTGGCTTGAGTATAATTTAGATTATAC  
AGAACTTGCCCTGCAGAACTGAAGGAGTCTGGAAAGCAGCACGGCTTTGCCTCTTCTC  
TGATTATTATTATAAGTGTCCTCGGCGGATTCTGTAAACATGAGTGGATTGATTACCAT  
CGTGGTACTCCTTGGGATCGCCTTTGTAGTCTATAAGCTGTTCTGAGTGACGGGCAGTA  
TTCTCCTCCACCGTACTCTGAGTATCCTCCATTTTCCCACCGTTACCAGAGATTCACCAA  
CTCAGCAGGACCTCCTCCCCCAGGCTTTAAGTCTGAGTTCACAGGACCACAGAATACTGG  
CCATGGTGCAACTTCTGGTTTTTGGCAGTGCTTTTACAGGACAACAAGGATATGAAAATTC  
AGGACCAGGGTTCTGGACAGGCTTGGGAACTGGTGGAATACTAGGATATTTGTTTGGCAG  
CAATAGAGCGGCAACACCCTTCTCAGACTCGTGGTACTACCGTCTTATCCTCCCTCCTA  
CCCTGGCACGTGGAATAGGGCTTACTCACCCCTTCATGGAGGCTCGGGCAGCTATTCGGT  
ATGTTCAAACCTCAGACACGAAAACCAGAACTGCATCAGGATATGGTGTTACCAGGAGACG  
ATAAAGTAGAAAAGTTGGAGTCAAACACTGGATGCAGAAATTTTGGATTTTTCATCACTTT  
CTCTTTAGAAAAAAGTACTACCTGTTAACAATTGGGAAAAGGGGATATTCAAAAGTTCT  
GTGGTGTTATGTCCAGTGTTAGCTTTTTGTATTCTATTATTTGAGGCTAAAAGTTGATGTG  
TGACAAAATACTTATGTGTTGTATGTGAGTGTAAACATGCAGATGTATATTGCAGTTTTTG  
AAAGTGATCATTACTGTGGAATGCTAAAAATACATTAATTTCTAAAACCTGTGATGCCCT  
AAGAAGCATTAAAGAATGAAGGTGTTGTACTAATAGAACTAAGTACAGAAAATTTAGTT  
TTAGGTGGTTGTAGCTGATGAGTTATTACCTCATAGAGACTATAATATTCTATTTGGTAT  
TATATTATTTGATGTTTGCTGTTCTTCAAACATTTAAATCAAGCTTTGGACTAATTATGC  
TAATTTGTGAGTTCTGATCACTTTTGAGCTCTGAAGCTTTGAATCATTCAGTGGTGGAGA  
TGGCCTTCTGGTAACTGAATATTACCTTCTGTAGGAAAAGGTGGAAAATAAGCATCTAGA  
AGGTTGTTGTGAATGACTCTGTGCTGGCAAAAATGCTTGAAACCTCTATATTTCTTTCGT  
TCATAAGAGGTAAAGGTCAAATTTTTCAACAAAAGTCTTTTAATAACAAAAGCATGCAGT  
TCTCTGTGAAATCTCAAATATTGTTGTAATAGTCTGTTTCAATCTTAAAAAGAATCA

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**FIGURE 326**

MAAACGPGAAGYCLLLGLHLFLLTAGPALGWNDPDRMLLRDVKALTLHYDRYTTSRRLDP  
IPQLKCVGGTAGCDSYTPKVIQCQNKGDGYDVQWECKTDLDIAYKFGKTVVSCEGYESS  
EDQYVLRGSCGLEYNLDYTELGLQKLKESGKQHGFAFSFYKSSADSCNMSGITIV  
VLLGIAFVVYKLFSLDGQYSPPPYSEYPPFSHRYQRFTNSAGPPPPGFKSEFTGPQNTGH  
GATSGFGSAFTGQQGYENSGPGFWTGLGTGGILGYLFGSNRAATPFSDSWYYPSYPPSY  
GTWNRAYSPLHGGSGSYSVCSNSDTKTRTASGYGGTRRR

**Signal peptide:**

amino acids 1-30

**Transmembrane domain:**

amino acids 171-190

**N-glycosylation site:**

amino acids 172-176

**Glycosaminoglycan attachment sites:**

amino acids 244-248, 259-263, 331-335

**Tyrosine kinase phosphorylation site:**

amino acids 98-106

**N-myristoylation sites:**amino acids 68-74, 69-75, 131-137, 241-247, 247-253, 266-272,  
270-276, 278-284, 312-318

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**FIGURE 327**

GGCACGAGGTGGAAGGGCTTTTACAAACAGATTGCTGGCCCCACCCCCCAGAATTTCTCA  
TCAGGAGTGGGCAAGACCAATCATTTGCATTTCTGACAAGTTCCCAGGAGCTGCAGCTGC  
TGGCCCTGGAACCACACTTTGAGAACCACTGCTTTAGACCAAACACCAAAGGAAGATGCA  
GCCACCCTCCTTTACATGTCACAACGCTCAGGGTCCATGAGTACCTCAGGCTGTCCAGCT  
GAGCTCCACCTGCAGCAGCCGAGATTCCCGACTCGCTCCACCATTGGGGGCTAGGAGTGA  
AGCGTGTACCAATGGTCAGCTCATGGCCAGCCAGGAAAGCCTCTCTGCTGTGCGTCTGTG  
CAGTTCTTGTTCTTCCCTGGAGGACTCTTGATCGCCTGTGATCTTGCCAGGAGACCAG  
GTGCCTGGGTCCCTTCCTGGAAGGGGACAAGTTACACACCCAGCCCCATTTTCCCACCA  
ACTTCTACATGCCTTGGAAGAACCTTCTACATGTTGGCTGCCCCCTTCCCCTATTTTCAGC  
AGTGCCAGTCCTGCTTATAAACCTGAGGCCTGCTCCCCATACCTTCCCTGTGCAAGTGC  
CAGCCGTTATTCCAGGCAGCCCAATGTTGTTGAGGCCAGATGGATTCTTGAAGCAGCTG  
GCCCATGGATGTGAGTCATCACAGTATTCTAGAAACAGAGAAGAGGTCTTAACCTAATGC  
GCATAGAGAAATTGTTCTCATTGTAAACATACCCCTGTCCTTAGCTGATCTAGGTGGAAG  
CCCAGCTTCATGTGCTAGGGGGCATGATAATGATAATAAAGGAATTGTATCTAGGACTAA

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## FIGURE 328

MVSSWPARKASLLCVC AVL VLPWRTL GSPVILARRPGAWVPSWKGTSYTPQPHFPTNFYM  
PWENLLHVGCP LPLFQQCPVLLINLRPAPHTFPVQVPAVIPGSPMLLRPDGFLEAAGPWM

**Signal peptide:**  
amino acids 1-27

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**  
amino acids 8-12

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**FIGURE 329**

CAAAGAGTAGTCAGTCCCTTCTTGGCTCTGCTGACACTCGAGCCCACATTCCATCACCTG  
CTCCCAATCATG CAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTC  
TGCAACCAGGTCTCTCTGCACCACTTGCTGCTGACACGCCGACCGCTGCTGCTTCAGC  
TACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTGAGACGAGCAGCCAG  
TGCTCCAAGCCCAGTGTTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCC  
AGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCCTGAGGGGTCCAG  
AAGCTTCGAGGCCCGAGCGACCTCAGTGGGCCAGTGGGGAGGAGCAGGAGCCTGAGCCTT  
GGGAACATGCGTGTGACCTCTACAGCTACCTCTTCTATGGACTGGTTATTGCCAAACAGC  
CACACTGTGGGACTCTTCTTAACTTAAATTTTAAATTTATTTATACTATTTAGTTTTTATA  
ATTTATTTTTGATTTACAGTGTGTTTGTGATTGTTTGCTCTGAGAGTCCCCCTGTCCC  
CTCCCCCTTCCCTCACAGTGTGTCTGGTGACAACCGAGTGGCTGTTCATCGGCCTGTGTAG  
GCAGTCATGGCACCAAAGCCACCAGACTGACAAATGTGTATCAAATGCTTTTGTTCAGGG  
CTGTGATCGGCCTGGGGAAATAATAAAGATGTTCTTTTAAACGGTAAAAAA

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**FIGURE 330**

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSTSRQIPQNFIADYFETSSQCSK  
PSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA

**Signal sequence:**

1-23

**Small cytokines (intercrine/chemokine) C-C subfamily  
signature:**

1-35, 2-36, 10-44, 34-74, 50-90

**Small cytokines (intecrine/chemokine):**

24-89



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**FIGURE 331**

GGCACGAGGTGAGACTTTAAATGAAATGTCTCACAAGCTAGGTGATCCAGGTTTTGTGGT  
CTTTGCAACCCTTGTGGTCATTGTGGCCTTGATATTAATCTTCGTGGTGGGTCCTCGCCA  
TGGACAGACAAACATTCTTGTGTACATAACAATCTGCTCTGTAATCGGCGCGTTTTTCAGT  
CTCCTGTGTGAAGGGCCTGGGCATTGCTATCAAGGAGCTGTTTGCAGGGAAGCCTGTGCT  
GCGGCATCCCCTGGCTTGGATTCTGCTGCTGAGCCTCATCGTCTGTGTGAGCACACAGAT  
TAATTACCTAAATAGGGCCCTGGATATATTCAACACTTCCATTGTGACTCCAATATATTA  
TGTATTCTTTACAACATCAGTTTTAACTTGTTTCTAGCTATTCTTTTAAAGGAGTGGCAAGA  
TATGCCTGTTGACGATGTCATTGGTACTTTGAGTGGCTTCTTTACAATCATTGTGGGGAT  
ATTCTTGTGTGCATGCCTTTAAAGACGTCAGCTTTAGTCTAGCAAGTCTGCCTGTGTCTTT  
TCGAAAAGACGAGAAAGCAATGAATGGCAATCTCTCTAATATGTATGAAGTTCTTAATAA  
TAATGAAGAAAGCTTAACCTGTGGAATCGAACAACACACTGGTGAAGTGTCTCCCGAAG  
AAATGGAAATCTGACAGCTTTTTTAAGAAAGGTGTAATTAAAGGTTAATCTGTGATTGTTA  
TGAAGTGAATTTGAATATCATCAGAATGTGTCTGAAAAAACATTTGTCCTCAAATAATGTT  
CTTTAAAGGCAATCTTTTTAAAGATTTCACTAATTTGGACCAAGAAATTACTTTTCTTGT  
ATTTAAACAAACAATGGTAGCTCACTAAAATGACCTCAGCACATGACGATTTCTATTAAC  
ATTTTATTGTTGTAGAAGTATTTTACATTTTCATCCCTTCTCCAAAAGCCGAATGCACTA  
ATGACAGTTTTAAGTCTATGAAAATGCTTTATTTTTTCATTGGTGATGAAAGTCTGAAAT  
GTGCATTTGTCTATCCCCACTCCATCAATCCCTGACCATGTAAGGCTTTTTTATTTTAAAA  
AAACAGAGTTATCCCAATACATTATCCTGTGATTTACCTTACCTACAAAAGTGGCTCCTG  
TTTGTTTGTATGATGATTGGTTTTATTTTTGAAATATTTATTAAGGGAAAATAAGTTACT  
GAATGAAGGAACCTCTTTCTTACAAAACAAAAAAGGGCAGAAATCACCCCAAGGAACG  
ATTTCTCAGGTTGAGATGATCACCGTGAATCCGGCTTCCTCTGAGCATTGATGGCCTTA  
GCACCTCATCAAGCCAGCACATCCTGCCTGCTGTTGCAGCCTGGCTGGGTTTTATTCTTCA  
GTTACCCCTAATCCCATGATGCCTGGAACCTTGATTACCGTTTTACATCAGCTCTTGTA  
TTTCAGTATATTTTCATAATGAGTTATATTGTCATTTAGACTTTGAACAGCTCTGGGAAA  
TAGAAGACTAGGTTGTTTCTTAAATTTAGCTCATGTTATAATAAAAAGTTGAAATG

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**FIGURE 332**

MSHKLGDPGFVVFATLVVIVALILIFVVGPRHGQTNILVYITICSVIGAFSVSCVKGLGI  
AIKELFAGKPVL RHPLAWILLLSLIVCVSTQINYNLRALDIFNTSIVTPIYYVFFTTSVL  
TCSAILFKEWQDMPVDDVIGTLSGFFTIIIVGIFLLHAFKDVSFSLASLPVSFRKDEKAMN  
GNLSNMYEVLNNNEESLTCGIEQHTGENVSRNGNLTA

**Signal sequence:**

1-33

**Transmembrane domain:**

40-60, 70-90, 103-123, 139-159

**N-glycosylation site:**

103-106, 182-185, 208-211, 215-218

**N-myristoylation site:**

57-62, 140-145, 181-186, 214-219

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**FIGURE 333**

[illegible]

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**FIGURE 334**

MAAGDGDVKLGTLGSGSESSNDGGSESPGDAGAAAEGGGWAAAALALLTGGGEMLLNVAL  
VALVLLGAYRLWVRWGRRGLGAGAGAGEESPATSLPRMKKRDFSLEQLRQYDGSRNPRIL  
LAVNGKVFDVTKGSKFYGPAGPYGIFAGRDA SRGLATFCLDKDALRDEYDDLSDLNAVQM  
ESVREWEMQFKEKYDYVGRLLKPGEEPSEYTDDEEDTKDHNKQD

**Signal sequence:**

None

**Transmembrane domain:**

45-65

**Tyrosine kinase phosphorylation site:**

202-210

**N-myristoylation site:**

11-16, 16-21, 37-42, 38-43, 79-84, 81-86, 83-88, 144-149

**Amidation site:**

75-78



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**FIGURE 336**

TGRGYCGDHESSFGAMEEPGATPQPYLGLLLEELRRVVAALPEGMRPDSNLYGFPWELVI  
CAAVVGFFAVLFFLWRSFRSVRSRLYVGREKKLALMLSGLIEEKSLLLEKFSLVQKEYEG  
YEVESLKDASFEKEATEAQSLATCEKLNRSNSELEDEILCLEKELKEEKSXHSEQDEL  
MADISKRIQSLEDESKSLKSQVAEAKMTFQIFQMNEERLKIAIKDALNENSQQLQESQKQL  
LQEAENVWKEQVSELNKQKVTFFEDSKVHAEQVLNDKESHIKTLTERLLKMKDWAAMLGEDI  
TDDDNLELEMNSESENGAYLDNPPKGALKKLIHAAKLNASLKTLEGERNQIYIQLSEVDK  
TKEELTEHIKNLQTQQASLQSENFHFNENQKLQQKLKVMTELYQENEMKLHRKLTVEEN  
YRLEKEEKLKSKVDEKISHATEELETYRKRAKDLEEEELERTIHSYQGQII SHEKKAHDNWL  
AARNAERNLNDLRKENAHNRQKLTETELKFELLEKDPYALDVPNTAFGRGSRGPGNPLDH  
QITNERGESSCDRLTDPHRAPSDTGSLSPPWDQDRMMFPPPGQSYPDSSALPPQRQDRFC  
SNSGRLSGPAELRSFNMPSLDKMDGSMPSSEMRNDTKDDLGNLNVDPSSSLPAENEATG  
PGFVPPPLAPIRGPLFPVDARGPFLRRGPPFPPPPPGAMFGASRDYFPFRDFPGPPPAF  
AMRNVYPPRGFPYLPFRPGFFPPPPHSEGRSEFPSPGLIPPSNEPATEHPEPQOET

**Signal sequence:**

None

**Transmembrane domain:**

54-74

**N-glycosylation site:**

150-153, 338-341, 636-639

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

413-416

**Tyrosine kinase phosphorylation site:**

414-421

**N-myristoylation site:**

466-417, 625-630, 697-702

**Leucine zipper pattern:**

142-163

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**FIGURE 337**

GGACTGCGGTCTCGGGCAGCAATGGCCGAGAAGCGCGACACACGGGACTCCGAAGCCCAG  
CGGCTCCCCGACTCCTTCAAGGACAGCCCCAGTAAGGGCCTTGGACCTTGGCGATGGATT  
TTGGTGCGGTTCTCATTCTTATTCACCGTTATAACTTTCCCAATCTCAATATGGATGTGC  
ATAAAGATTATAAAAGAGTATGAAAGAGCCATCATCTTTAGATTGGGTGCGATTTTACAA  
GGAGGAGCCAAAGGACCTGGTTTGTATTTTATTCTGCCATGCACTGACAGCTTCATCAAA  
GTGGACATGAGAACTATTTCAATTTGATATTCCTCCTCAGGAGATCCTGACAAAGGATTCA  
GTGACAATTAGCGTGGATGGTGTGGTCTATTACCGCGTTCAGAATGCAACCCTGGCTGTG  
GCAATATCACCAACGCTGACTCAGCAACCCGTCTTTTGGCACAACACTACTCTGAGGAAT  
GTTCTGGGCACCAAGAATCTTTCTCAGATCCTCTCTGACAGAGAAGAAATTGCACACAAC  
ATGCAGTCTACTCTGGATGATGCCACTGATGCCTGGGGAATAAAGGTGGAGCGTGTGGAA  
ATTAAGGATGTGAAACTACCTGTGCAGCTCCAGAGAGCTATGGCTGCAGAAGCAGAAGCG  
TCCCGCGAGGCCCGCGCCAAGGTTATTGCAGCCGAAGGAGAAATGAATGCATCCAGGGCT  
CTGAAAGAAGCCTCCATGGTCATCACTGAATCTCCTGCAGCCCTTCAGCTCCGATACCTG  
CAGACACTGACCACCATTGCTGCTGAGAAAACTCAACAATTGTCTTCCCTCTGCCATA  
GATATGCTGCAAGGAATCATAGGGGCAAAACACAGCCATCTAGGCTAGTGTAGAGATGAG  
CGCTAGCCTTCCAAGCATGAAGTCGGGGACCAATTAGCCTTTAACTCATAAAGAGAGGG  
TAGGGCTTTTTCTTTTTCCATATGTCAATTGTGGTGTTCCCAGAATGTATAGCAGTTATAA  
AAATAGGTGAAAGAATTGTTAGCTTGTAATACTGAGAGATTGGTGATTTATATAAGGTA  
ATCTGTTAGTCTTAAATAGTTAAAGTTTGTATTTTTTAGATTATTATGTAGTAGGTTAG  
ATCCCTCTTGTTTTGACTTCCACTGACTCATTCTGAACCCCTAAGCACCCAGGCCACAG  
GCAAGAACCTGGGCTGTAAGTCCACCTGACACCGCTGACTGGCTAAATGCTTTGCAGAA  
AGTGATGACCTTACACCACAACCAGCTTCTCCAGGTCATATGTGCCTTACCTCCAGAAGT  
CTTTTTTTTTTTTTTTTTTCTGAGATGGAGTTTCACTCTTGTTGCCCAGGCTGGAGTGCAA  
TAGCATGATCTCGGCTCACTGCAACCTCCGCCTCCTGGGTTCAAGAGATTCTCCTGCCTC  
AGCCTCCCCAGTAGCTGGGATTACAGGCTCATGCCACCATGCCAGCTAATTTTTGTATT  
ATTATTATTGTTTTTTAGTAGAGACGGGGTTTCAACCATGTTGGCCAGGCTAGTCACGAAC  
TCCTAACCTCAGGTGATCCACCCACCTCTGCCTCCAAAGTGCTGGATTACAGGCTGAGCT  
ACCACCTGGTTTGGAGAGTCTTAATTAATTGAAATTTCCCTAATGTTCAATTTATTTTCT  
AAATCCAGCCGTGTTTTAGAATAATCCTTACTTGAGAGTAGCCATTTTCTTGTGTACTTG  
TCAGAACTAGAGGAAATAGCCAAGACTAATGAAAAACATTACTCTAACCTTAAAAGACT  
TTTAAATTCACTACTAGAGTGGTCATTTTAAAATACATCCATGTTTTAACTTATTTTGA  
GCCTTCTTTTTATGAGTAAATGATTCCTCCTGTTCTGTCTTCAAACCAGCTAAATATT  
TGTCACAAAAGTGACTTTTTTCTCACTGTTGCCTATTTTCATATATCAGGTTTTAAATAG  
TTTTAATTTTTTAATAAAATTTTTCTCTACGTTCTATATGCAATTGTTATATATCTATTT  
GAATAGCTGAAGGACTAAAATACTTTTTTAAGAGATAACTTCAGGAAACCATTATATTTT  
ACTATCTGCATGCTGTAACTGTGGTACACTGTGAAATATGTTGATTACAAACCCATTCA  
TTACATAGTATAAGGAATTCACAGTATATTGACTATATAGTGTCTAATGACTGGGCAGAT  
ACTGTCAACTTACAATATCTATATAGAGAGGCTTTAACTTACCTTACTCATTCTCTATG  
ATGTATGACTTGATGCTGAAAGAGGAAGCTGGTCAGCTCCTCATGGACAACAAATCTTA  
GTCTATAATATTAGGAGACATCTCTAGTTTTGCAATGTCTGTGAATCTGAGCAACCTGG  
ACTTCTGCTTACTGGCCAGAAAGCTGGCGGGTGACATTTGTAACATTTCTCTTTGAGAC  
TCTGAGTTACCTAGAGAAGTCTAAGCATAACAGCTTTCTTTCCCAGCACGAGCCTTTAT  
AGCTCTCTTTAGCTCAACCACTCTGTCCATCCAGCCAATGGATGTCTTCCCTGTACCCA  
ATTCAGCTTATTTTAGGGAAGCCTTGAACTACCATGTATCTGGCTCTAGCTGAGTTAT  
TGAGGATTGAGCCAGTGCAACGTTAACTCAGTGCATTACATTTGATTTAAATGATGGT  
TTTATCTGTTGTGTGAAGTGGTTCACCCTTGAGGACCAGGAGCCTCCATATCCTGACTGA  
AAACCTTTTCTGAGACTTAGAGTAACAGTACTTTTGGTTCCTTGAGTTCTCCTGTCTCCA  
GATACCTAAATGACCTTGACTTTTTCTGCCTTGTTGAATTCGTAGTCCAATCAGCTGAAATT  
AAATCACTTGGGAGGGACGCATAGAAGGAGCTCTAGGAACACAGTGCCAGTGCAGAAGTT  
TCTCCAGGTGGCCTCCCTTTCCAACAATGTACATAATAAAGTGTATGCACCTTCACT

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**FIGURE 338**

MAEKRDTRDSEAQRLPDSFKDSPSKGLGPCGWILVAFSFLFTVITFPISIWMCIKIKEY  
ERAIIFRLGRILQGGAKGPGLFFILPCTDSFIKVD MRTISFDIPPQEILTKDSVTISVDG  
VYYRVQ NATLAVANITNADSATRLLAQTTLRNVLG TKNLSQILSDREEIAHNMQSTLDD  
ATDAWGIKVERVEIKDVKL PVQLQRAMAAEAEASREARAKVIAAEGEMNASRALKEASMV  
ITESPAALQLRYLQTLTTIAAEKNSTIVFPLPIDMLQGIIGAKHSHLG

**Signal sequence:**

1-45

**Transmembrane domain:**

None

**N-glycosylation site:**

128-131, 135-138, 159-162, 229-232, 264-267

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

4-7

**N-myristoylation site:**

26-31, 278-283, 281-286

**SPFH domain/Band 7 family:**

39-230



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**FIGURE 339**

TCTAGAGCCCTCTCCCAACATGGCGGCCTCAGCAAAAAAGAAGAATAAGAAGGGGAAGAC  
TATCTCCCTAACAGACTTTCTGGCTGAGGATGGGGGTACTGGTGGAGGAAGCACCTATGT  
TTCCAAACCAGTCAGCTGGGCTGATGAAACGGATGACCTGGAAGGAGATGTTTCGACCAC  
TTGGCACAGTAACGATGACGATGTGTATAGGGCGCCTCCAATTGACCGTTCCATCCTTCC  
CACTGCTCCACGGGCTGCTCGGGAACCCAATATCGACCGGAGCCGTCTTCCCAATCGCC  
ACCCTACACTGCTTTTCTAGGAAACCTACCCTATGATGTTACAGAAGAGTCAATTAAGGA  
ATTCTTTCGAGGATTAAATATCAGTGCAGTGCCTTTACCACGTGAACCCAGCAATCCAGA  
GAGGTTGAAAGGTTTTGGTTATGCTGAATTTGAGGACCTGGATTCCCTGCTCAGTGCCCT  
GAGTCTCAATGAAGAGTCTCTAGGTAACAGGAGAATTCGAGTGGACGTTGCTGATCAAGC  
ACAGGATAAAGACAGGGATGATCGTTCCTTTGGCCGTGATAGAAATCGGGATTCTGACAA  
AACAGATACAGACTGGAGGGCTCGTCCTGCTACAGACAGCTTTGATGACTACCCACCTAG  
AAGAGGTGATGATAGCTTTGGAGACAAGTATCGAGATCGTTATGATTACAGACCGGTATCG  
GGATGGGTATCGGGATGGGTATCGGGATGGCCACGCCGGGATATGGATCGATATGGTGG  
CCGGGATCGCTATGATGACCGAGGCAGCAGAGACTATGATAGAGGCTATGATTCCCGGAT  
AGGCAGTGGCAGAAGAGCATTTGGCAGTGGGTATCGCAGGGATGATGACTACAGAGGAGG  
CGGGGACCGCTATGAAGACCGATATGACAGACGGGATGATCGGTTCGTGGAGCTCCAGAGA  
TGATTACTCTCGGGATGATTATAGGCGTGATGATAGAGGTCCCCCCCCAAAGACCCAACT  
GAATCTAAAGCCTCGGAGTACTCCTGAAGAAGATGATTCCTCTGCTAGTACCTCCAGTC  
CACTCGAGCTGCTTCTATCTTTGGAGGGGCAAAGCCTGTTGACACAGCTGCTAGAGAAAG  
AGAAGTAGAAGAACGGCTACAGAAGGAACAAGAGAAGTTGCAGCGTCAGTGGAAATGAGCC  
AAAAGTAGAACGACGGCCTCGGGAGAGACACCCAAGCTGGCGAAGTGAAGAACTCAGGA  
ACGGGAACGGTCGAGGACAGGAAGTGAGTCATCACAACTGGGACCTCCACCACATCTAG  
CAGAAATGCACGAAGGAGAGAGAGTGAGAAAGTCTCTAGAAAATGAAACACTCAATAAGGA  
GGAAGATTGCCACTCTCCAACCTCTAAACCTCCCAAACCTGATCAGCCCCCTAAAGGTAAT  
GCCAGCCCCCTCCACCAAAGGAGAATGCTTGGGTGAAGCGAAGTTCTAACCCCTCCTGCTCG  
ATCTCAGAGCTCAGACACAGAGCAGCAGTCCCCTACAAGTGGTGGGGGAAAAGTAGCTCC  
AGCTCAACCATCTGAGGAAGGACCAGGAAGGAAAGATGAAAATAAAGTAGATGGGATGAA  
TGCCCCAAAAGGCCAACTGGGAACTCTAGCCGTGGTCCAGGAGACGGAGGGAACAGAGA  
CCACTGGAAGGAGTCAGATAGGAAAGATGGCAAAAAGGATCAAGACTCCAGATCTGCACC  
TGAGCCAAAAGAAACCTGAGGAAAATCCAGCTTCTAAGTTCAGTTCGCAAGCAAGTATGC  
TGCTCTCTCTGTTGATGGTGAAGATGAAAATGAGGGAGAAGATTATGCCGAATAGACCTC  
TACATCCTGTGCTTTTCTCCTAGTTTCTCTCCACCCTGGAACATTTCGAGAGCAAATCAA  
ACCTCTATCCAGACAAGACAAAATAAACTCAACATCTCCTGAAGACCTTTCTTACCTTT  
TTTTAAAAACAAAAXTGAAATTATTTTGCATGCTGCTGCAGCCTTTAAAGTATTGAAGT  
AACTGGAGAATTGCCAATACAGCCAGAGAGAAAGGGACTACAGCTTTTTAGAGGAAAAGT  
TGTGGTGCGTTATGTACCATGCAGTTGCCAGTGTGATTAGTGCCTAGGGGTCTCATTTA  
GCAGAAATGGTAATGACAGTGATATAATGCCTGGAACCTGGTTGGGCAGTAGGGGAGGGA  
GGTAGAAGGAAAAGTGTGAGATTTCTACCTTTTAGTTTTTCATCCTATTGTGGCATATATG  
AATTCTCAAACATTATCTGAATAAAATTTTCCACTCTTGGAAGGTAGATTTAGCCTCAAG  
TTGTTCTAGTCTCCAGGAGGCTGCCAGCCCCCTCCTCTTATTTAATTCTGAGTTTTGGGGG  
CCAGCCTAGAGGGAATTCCTTTTTTTTTTTTTTTTAAACCCCCAGGGGGTAGTTGGGAGT  
GAGACTATAGGCCATAAAGAATGGGACTGCATTTGGACCAAATAAATGGGAAAATCGTGG  
TTTGAAAAGAAGCTTTTTGGGAAGTGATGAGTCATTTTGCACCAGGTAATAGGGGAAAATT  
GTGTGACCTCCAGCAAACACATGAATGGTTATTTCTGGAGCCGGAAGCACTTGGGGGTC  
GTGGTAATTCCCAGTGTTTTCTGTGTCCTAGTTTTTACCCTTTCTAAACACTGTCCTTTTTT  
GAAAGTTTGAATATATCCACATTCTATTGAAACCTTGAACTAAAAATTTAGACTCTTA  
TCGTATCTTAAGTTCTTCATGCTACTCTTAACCTCCAAAAAGCAGTATCTAAGTCACA  
TACATGATGTCTTGGGCATTTTCTGAGCCATGGAGAACTCTGAAAGGAAGAATCGCTGCT  
TTTCTCAAGCAAATCGGTTTCTTGATGTCTTTTGGTTCTCCTTGCTCCTGCTCCTGATGCTT

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GGACCCCTTTTATTGATCAGAGTGCTCTAGAATAATGGATGGTCTTGGATGATGGATAAA  
TAGGGACAGGGACAGTTAAATTGGGAGCCTTTCTTACAACCTTGATGGGATTTTTTCCCCC  
CAAGTTTTCTTCTCCACTGAAATGCCACACTAATGCTTGTTGGATTTCATGAGGTGGCCAG  
ACCAATGTGTTGTTTTGTTGTTGTTTTTTTTTTAAGCTTCCCTTGAGAGAATAAATGGTA  
ATGGAGAGAATCATTAAACAAGGTCCTGGTTTTCTCTTGCAACACAGTAGCTAAACTTGCC  
TGCTTTTATATGCATTTTTGTAGGGATCAGCTTGGTAGACAGTATTAGCGGAGAAACACC  
TTGATCTTGGTTTGCAAGCCCTTCTCCCATCAGTCCTAGATTAGGCCCTGTTCCAGCCATG  
CAGGGGTGTTGGTTTATGCGTGCTGCAGCAGTGGGCATAATGAATATAATTTACCCAGTG  
GACAAAGGTGTGTACCAAGTGAATTTAAATAAATTGGTGTGGATTGGCCAGTAGCTAAGAA  
GTGGGCCTTTTAAAGAGTATTGAAGATTGAAAGGGTTTTTCTTTCTTTTTTAAAAAGAAA  
AACAAACTATTGATTGTAGATAATGAAAAGCTAGGGTTTTGCCCTCTTCATGTCTACTCTC  
CTTCCAAATAGTTATATCCAAAAGCTGTTTTTCCCTCTCCCCTACCTTGTCCCCCTATTA  
AAATAGAAACAGGGATTGATTAATGTCCCGCTCCTGAATACATGTAAATTTGTACAAAA  
ATATCTTCTATGAAAATGATTTGTAATCTGTAGACTTATTACCTGGGAGATGTCTTGATG  
TAAATCCCATCCTTTGGGTTGTGGGTTTTTTGTTTTCTCCAAATAAATCTGATCTTTAA  
AGTTAAAAAATAAATAAATACTCTAGAGTCGAGGAATTC

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**FIGURE 340**

MAASAKKKNKKGKTISLTDFLAEDGGTGGGSTYVSKPVSWADETDDLEGDVSTTWHSNDD  
DVYRAPPIDRSILPTAPRAAREPNIDRSRLPKSPPYTAFLGNLPYDVTEESIKEFFRGLN  
ISAVRLPREPSNPERLKGFYAEFEDLDSLLSALSLSNEESLGNRRIRVDVADQAQDKDRD  
DRSFGDRNRDSDKTDTDWRARPATDSFDDYPPRRGDDSFQDKYRDRYDSRYRDGYRDG  
YRDGPRRDMDRYGGDRYDDRGSRDYDRGYDSRIGSGRRAFGSGYRRDDYRGGGDRYED  
RYDRRDDRWSRRDDYSRDDYRRDDRGPQRPKLNLKPRSTPEEDDSSASTSQSTRAASI  
FGGAKPVDTAAREREVEERLQKEQEKLRQWNEPKLERRPRERHPSWRSEETQERERSRT  
GSESSQTGTSTTSSRNARRRESEKSLNETLNKEEDCHSPTSKPPKPDQPLKVMPPPPK  
ENAVVKRSSNPPARSQSSDTEQQSPTSGGGKVAPAQPSEEGPGRKDENKVDGMNAPKGQT  
GNSSRGPGDGGNRDHWKESDRKDGKKDQDSRSAPEPKPEENPASKFSSASKYAALSVDG  
EDENEGEDYAE

**Signal Sequence:**

None

**Transmembrane domain:**

None

**N-glycosylation site:**

120-123, 448-451, 542-545

**Glycosaminoglycan attachment site:**

507-510

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

439-442, 486-489

**Tyrosine kinase phosphorylation site:**

225-233, 264-270

**N-myristoylation site:**

25-30, 26-31, 28-33, 118-123, 421-426, 428-433, 538-543

**Amidation site:**

276-279, 522-525, 563-566

**Cell attachment sequence:**

215-217

**Eukaryotic putative RNA-binding region RNP-1 signature:**

137-144

**RNA recognition motif:**

98-168

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**FIGURE 341**

GCGTGGACACCACCTCAGCCCACTGAGCAGGAGTCACAGCACGAAGACCAAGCGCAAAGC  
GACCCCTGCCCTCCATCCTGACTGCTCCTCCTAAGAGAGATGGCACCGGCCAGAGCAGGA  
TTCTGCCCCCTTCTGCTGCTTCTGCTGCTGGGGTGTGGGTGGCAGAGATCCCAGTCAGT  
GCCAAGCCCAAGGGCATGACCTCATCACAGTGGTTTAAAATTTCAGCACATGCAGCCCAGC  
CCTCAAGCATGCAACTCAGCCATGAAAAACATTAACAAGCACACAAAACGGTGCAAAGAC  
CTCAACACCTTCCTGCACGAGCCTTTCTCCAGTGTGGCCGCCACCTGCCAGACCCCCAAA  
ATAGCCTGCAAGAATGGCGATAAAAACTGCCACCAGAGCCACGGGCCCCGTGTCCCTGACC  
ATGTGTAAGCTCACCTCAGGGAAGTATCCGAAGTGCAGGTACAAAGAGAAGCGACAGAAC  
AAGTCTTACGTAGTGGCCTGTAAGCCTCCCCAGAAAAAGGACTCTCAGCAATTCCACCTG  
GTTCTGTACACTTGGACAGAGTCCTTTAGGTTTCCAGACTGGCTTGCTCTTTGGCTGAC  
CTTCAATTCCCTCTCCAGGACTCCGCACCACTCCCCTACACCCAGAGCATTCTCTTCCCC  
TCATCTCTTGGGGCTGTTCTGGTTCAGCCTCTGCTGGGAGGCTGAAGCTGACACTCTGG  
TGAGCTGAGCTCTAGAGGGATGGCTTTTCATCTTTTGTGCTGTTTTCCAGATGCTTA  
TCCCCAAGAAACAGCAAGCTCAGGTCTGTGGGTTCCTGGTCTATGCCATTGCACATGTC  
TCCCCTGCCCCCTGGCATTAGGGCAGCATGACAAGGAGAGGAAATAAATGGAAAGGGGGC  
AAA  
AAA

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**FIGURE 342**

MAPARAGFCPLLLLLLLGLWVAEIPVSAKPKGMTSSQWFKIQHMQPSPQACNSAMKNINK  
HTKRCKDLNTFLHEPFSSVAATCQTPKIACKNGDKNCHQSHGPVSLTMCKLTSGKYPNCR  
YKEKRQNKSYVVACKPPQKKDSQQFHLVPVHLDRVL

**Important features of the protein****Signal peptide:**

1-22

**Transmembrane domain:**

none

**N-glycosylation site:**

127-131

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

139-143

**N-myristoylation site:**

18-24, 32-38

**Pancreatic ribonuclease family signature:**

65-72

**Pancreatic ribonuclease family proteins:**

49-93

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**FIGURE 343**

GCATTTGCCACTGGTTGCAGATCAGGCGGACGAGGAGCCGGGAAGGCAGAGCCATGTGGC  
TGCCCCCTGCTCTGCTCCTTCTCAGCCTCTCAGGCTGTTTCTCCATCCAAGGCCAGAGT  
CTGTGAGAGCCCCAGAGCAGGGGTCCCTGACGGTTCATGCCACTATAAGCAAGGATGGG  
AGACCTACATTAAGTGGTGGTGCCGAGGGGTGCGCTGGGATACATGCAAGATCCTCATTTG  
AAACCAGAGGGTTCGGAGCAAGGAGAGAAGAGTGACCGTGTGTCCATCAAGGACAATCAGA  
AAGACCGCACGTTCACTGTGACCATGGAGGGGCTCAGGCGAGATGACGCAGATGTTTACT  
GGTGTGGGATTGAAAGAAGAGGACCTGACCTTGGGACTCAAGTGAAAGTGATCGTTGACC  
CAGAGGGAGCGGCTTCCACAACAGCAAGCTCACCTACCAACAGCAATATGGCAGTGTTCA  
TCGGCTCCCAAGAGGAACCACTACATGCTCCTGGTATTTGTGAAGGTGCCCATCTTGC  
TCATCTTGGTCACTGCCATCCTCTGGTTGAAGGGGTCTCAGAGGGTCCCTGAGGAGCCAG  
GGGAACAGCCTATCTACATGAACTTCTCCGAACCTCTGACTAAAGACATGGCCACTTAGA  
GAGATGGATCTGCAGAGCCTTCTGCCCCGACGTTTCCAGAAGAGACTCGGGCTGTG  
GAAGGAACATCTACGAGTCCTCGGGATGCAGTGACTGAGATAGGGGGCCCTGGGCCTCCGC  
CCTGGCCTTGGAGCTGGTGGGCACCTCCCTGTTCTGCACAGCTCAGGGACTTAGCCAGGT  
CCTCTCCTGAGCCACCATCACCTCCTGGGGTGCCAGCACCTGTTCTCTTGGTCAGGAGCT  
GTAGAGATGGAGCTCAAGCACTGGACGACTCTGTCCCCACTGCTGGAATAACTCGGGCAC  
AGAGCATGGGACCAAGTACAGAAAGAGGTTGGGGGAGACCCCCCAGCCCTAGACTTCC  
ATCATTCGGGAGACCAACTCAACACCGTCTTTGCTGAGAACCTGATATATCCGTGTTTT  
TAAATTTTTTTTTTTCTAGCAAAGTTGGGTTTTAATGACTTATGTTTCATAGGAAACCTCT  
CTGATCCCACACACAAGGAGGGTGATCTGGGATGAGTTCCTGGTTCTAGGGCATGAGGG  
GCTGGATGGACCCTGTCCCCAGGGAGGACATGGCTCTGAGTCCACAGGGCTGAGGAGGCA  
ATGGGAACCTCCCTGGCCCCGGCCGGTGCTTGTCTCCCCCTCCACCTCTTCTCCTCCTC  
TAGCTCCCCAAGCTCCCTGCCTATTCCTCCCAAGAGCCTGTGAGGCCTCAAGAACCACCT  
CTCAGCATGACAGCTTGGGTCTCCTCCCCAAAAGAGCCTGTGAGGCCTCAAGAACCACCT  
CCAGGTGGGGAGGGCAGTAACGAAAACCATCGCAGGAAATGGCACCCCTCCCTTTTCGGTG  
ATGTTGAAATCATGTTACTAATGAAAACCTGTCTTAGGGAAGTGGTCTGTCTCCTCACAG  
GCTTCACCCACGGCGATGAGGCCCTTGAATGTGGTCACTTTGTGCTGTATGGTTGAGGGA  
CCCTCACACCAAAGGGACCTTCCCATGTGAGATGTGCTCCCGCCCCACCTGCCCCACAAG  
CAAACACACCACACATGTTTCGGCATGTTGCCCTTTGAACACCCATGAGGACGCCTCCAAC  
CTGCTCTTGGTTCTAATAGGGAGTACTGACTGTGAGCAGTGGATAAAGGAGAGGGGACCC  
TCTGGTCCCTAGCATGGCACCCAGAGCCTCCCTCTTCTTGTCTTCTCAGCCAAAGAGAAA  
CTTTCTCTGACTTTGAACTGAATTTAGGTCTCTGGCCAATGATGGGCCTGAAAATTCAT  
AATGGCCAGAGAGGAGAGTTCGAGCCCGGCTAAGATCCCCTGAGTCATTCTGTGAGGGAC  
CAAGACCCACAGTCCACCAGCCCCAGGGCCCTACCTCCTGGAATGCTTCTCTGGATCCAG  
CTTCCCGAAGATCCGACCAGACCCAGGGAGGACGGCACCGCTCCGCGGGAGGGAAAGCCA  
AAGCATGGTGCTTCACCAGCTGGACTCAGGGGCGAGGGGACATGGGCGCTTGTCAACGTG  
ATGTCATTCTTTTCCACCGTTTCTTCTGTTGATATTCAATGAATCCGTCAATCTCTCT  
GGGAAA

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**FIGURE 344**

MWLPPALLLLSLSGCF SIQGPESVRAPEQGS LTVQCHYKQGWETYIKWWCRGVRWDTCKI  
LIETRGSEQGEKSDRVSIKDNQKDRTFTVTMEGLRRDDADVWCGIERRGPD LGTQVKVI  
VDPEGAASTTASSPTNSNMAVFIGSHKRNHYMLLVFVKVPILLILVTAILWLKGSQRVPE  
EPGEQPIYMN FSEPLTKDMAT

**Important features of the protein:**

**Signal peptide:**

Amino acids 1-17

**Transmembrane domain:**

Amino acids 151-170

**N-glycosylation site:**

Amino acids 190-194

**Tyrosine kinase phosphorylation site:**

Amino acids 95-103

**N-myristoylation sites:**

Amino acids 66-72; 125-131

**Prokaryotic membrane lipoprotein lipid attachment site:**

Amino acids 5-16

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## FIGURE 345

CTGAGCTCCCGGGCTCCGGCAGCGCGCTGGCGGGGCGCCGCATTGCACACTCTGGGGGCG  
CCGCAGTGTTCGTGGGATGGGGCAGCGGGCTGCAGCTGGCGGCCGGAATCCGCGCGCAGC  
CCGGGTGCAAGTTCTCTCCTGTTGCCCTGAGTGCCCACTCCAGGCCCTCTGTATGAGTG  
ACACTTCAGTCTGCCATGGAACCTGGCCCTGCTCTGGCCTGGCTCCTGCTCCTGAGCCTG  
CTGGCGGATTGTCTGAAAGCTGCTCAGTCCCGAGACTTCACAGTGAAAGACATTATCTAC  
CTCCATCCTTCAACCACACCATATCCTGGTGGATTAAATGTTTACCTGTGAAAAGGCA  
GCAGACAATTATGAGTGCAACCGATGGGCTCCAGACATCTACTGCCCTCGAGAGACCAGA  
TACTGCTACACTCAGCACACAATGGAAGTCACAGGAAACAGTATCTCAGTCACCAAACGC  
TGTGTCCCCTGGAAGAGTGCTTATCCACTGGCTGCAGAGACTCCGAGCATGAAGGCCAC  
AAGGTCTGCACTTCTTGTGTGAAGGAAATATCTGTAACCTGCCACTGCCCCGAAATGAA  
ACTGATGCCACATTTGCCACGACGTACCTATAAATCAGACAAATGGGCACCCACGCTGT  
ATGTCAGTGATAGTGTCTGCTTGTGGTTGTGGTTAGGGCTCATGTTATAGTGGCTCAGT  
GGCTCCATGTGTAAATAGCGATCCATGGGGATCTCGATGGTCCACAGACCTGCATGAGTC  
ATTGGCCTGACAGTAATTACACATGTGAGACACAACACTCTTGGAGGTCAACAGCCAA  
GCATTGCCACTTACCATGAGGAATAAATGTTGCTTCATTGTAGCCATTTTGTGCTAACC  
GAGACTCATCAAAGCCTTCTGTCAGTACAGCCCAAGTTCCATACCATAAACGTTTGT  
CATTCCAAGAAGTAGTTCTGCATTTATCGAGATCTGGGGTCTTAATTTGGAAGAATACA  
TGCATGAGATGCAGTAGGTCTGAGACTGTAAGATATTAGGAGTATGTTATAGGGGCATG  
TATAGATGTGGGCTTTTTCAGGAGAAAAGTAACCATTGGTTTAAATATAATCATGAGTTCA  
TTTGTAGCTTTAGAAATTTTAAAACATTGACTCCAACTGAATGGACTATTTCTTGGAAA  
TTCTGACTGAGTCCCTGGAAGAGTAGTAATTCCAACAATTCAGCCATTTGTTCATTA  
TTTTCCCAACATTCCTCTCCAGTGCTGGGAATCACATTTCTCTGTTCTGTGCAGAAGA  
CAAAAAGGCAATCATAAAAGTTTGTATATTTGTGGGGGTGCCTGGAGGAGGATTTTCT  
CAACTTAATGGAGCCACTGTCCATAAAGTGGCTGTTATCCCTTCATATAATTGGTGAGAT  
CAGCCTTCTCCTTGACTTGGCACCTAATTATGCTTCATGAGATCCTAGATTCCACCTGAG  
TCAATTGTGTCCAGAGCCCCAAACCAGGATGGAGTTGTTTCCCAGATATGGGGTTCTA  
TTCAGCCATAGATAATCTAGACAGAGGATTTCAGAATGAAAGGAAAAATGTGTGGAGATT  
AGTCCTAGTTTCACTCTGAGGGCCGACTAAGTGGCTCAGCCAGCTTCTTACTCCATCTGCA  
GTTTCACTGCCAAAGAGCTCCCACTTCCAAATCCCAGTGACTTTATGGAGAAGATTCT  
GCATTAAATTGTCTTTCGAATGATGGGGAAGCAAGGCATAATATGCGATGATGAGGAGAA  
AGTAGACCAGTGAGGTGATTGCAAGACTAACAAGGAGACTCAATGGGAAGTTTCTTCT  
TTTTAGATATTGCTTTTGAAGTAGATGGTAAAATTTTGTGTCATCCTTCTGTATTTTTTG  
TACCCCAAGTTACAATTTTTCTTCTTCTTGTAAATAATTTAAACAGTATTTATTTTTGT  
AAGGCATAACTAGAACTAAAATATATTCTAAAAAATTCATTATTCTGAACAAAGTGATC  
AAATTAGAATACATATTTTTCAACAGTGGTAGAGCTTTTAATATATGTTTATTGAAAGTT  
ATCTATAATACTTGCAACAGTGTTGAAAAAGTTAACATGTAGGCAAGAGCAATATGTTT  
GTCTCAAGGATTTTTCCATGGTTTCTCAGTGATGGTGTCTGGAATTATTCAGGTGGTG  
ACCATCACTGGTCTAAGTTTGTGTGCAGGGTTTTTCAGACGTGTTTTGTGAACTTGGTA  
GAACCATGGCTAATAAAGAGGACAGTGTTGTCAGGGTCCATCTGCCCTCCATAGAAAAAT  
GTCTCTGGCTCATAAAATGAGACTCCCTCAGGGACTAAATATGAACTGACAGCAGTAACT  
CTGATACAGAATAATCTAAATTGCATCAAATGGCCTTAATTCAGAGTTTGTAGGCTTAT  
CAGTATGTTGCTTTTAAATTGGGGTGGGAAAGTAGAGGGAGAGAAAGCAAGACATTTATTA  
AGCACCTCGTATGTGCCAGGCACTATGCTAAGCACTTACATAAGTTAGGATTAATCCCT  
GCAAGAATCCTATAAAGAATGTTACTAGCATTTACACTTCCCAAATGAAGGTACCAAAGC  
TCAAACGCAATGTTGTGAAGCTGTTTCTTTCAGATTTAGGTTATGTGGGATGATGTGGGA  
TTGAAGAGGAAAGAAAGGTGGGATTATCCCCCTAGGAAGACTTTCAGGCCTGACTTCATA  
GGAATTCATCCATCTTATCATGTGGAGTTTATCTCACCCCTGCTGTTGCAGGATGCTATTT  
GCATGTGTCCCAGGTGATGTTTTTCTTTGGGGAGTAGGGGTTTGGCTTCTCATTTCAT



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CCCTCTTGCTAAAGAGGAGATAGTTGATGTTGCATCTAAAGATGCTATAAGACAATGAAAGTTTGATGTTGTAC  
ATACCTACAAGTACCATTTTTTGTGCATGATTACACTCCACTGACATCTTCCAAGTACTAC  
ATGTGATTGAATAAGAAACAAGAAAGTGACCACACCAAAGCCTCCCTGGCTGGTGTACAG  
GGATCAGGTCCACAGTGGTGCAGATTCAACCACCACCCAGGGAGTGCTTGCAGACTCTGC  
ATAGATGTTGCTGCATGCGTCCCATGTGCCTGTCAGAATGGCAGTGTTTAATTCTCTTGA  
AAGAAAGTTATTTGCTCACTATCCCCAGCCTCAAGGAGCCAAGGAAGAGTCATTACATG  
GAAGGTCCGGGACTGGTCAGCCACTCTGACTTTTCTACCACATTAAATTCTCCATTACAT  
CTCACTATTGGTAATGGCTTAAGTGTAAGAGCCATGATGTGTATATTAAGCTATGTGCC  
ACATATTTATTTTGTAGACTCTCCACAGCATTATGTCAATATGGGATTAATGCCTAAACT  
TTGTAAATATTGTACAGTTTGTAATCAATGAATAAAGGTTTTGAGTGTAATAAAAAAAAAA  
AAAAAA

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**FIGURE 346**

MEPGPALAWLLLLLLADCLKAAQSRDFTVKDIIYLHPSTTPYPGGFKCFTCEKAADNYE  
CNRWAPDIYCPRETRYCYTQHTMEVTGNSISVTKRCVPLEECLSTGCRDSEHEGHKVCTS  
CCEGNICNLPLPRNETDATFATTSPINQTNHPRCMSVIVSCLWLWLGLML

**Important features of the protein:**

**Signal peptide:**

1-22

**Transmembrane domain:**

None

**N-glycosylation site:**

134-138, 147-151

**N-myristoylation site:**

45-51, 87-93, 106-112, 124-130

**Ly-6 / u-PAR domain protein:**

115-128

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**FIGURE 347**

GATCAAGCGCCTTCCTTTCCCTTCCTCTCCCTACTTGGCCTTTGCCCTAAGCCAAGACCT  
GGCCATCAGCCTGGCTGCAGGGGCTGCAGAGCCAGCTGCACCTTTTTCAGGTATGGGGGA  
GGGCCAGGCACCATGAAGCCAGTGTGGGTGCGCCACCCTTCTGTGGATGCTACTGCTGGTG  
CCCAGGCTGGGGGCCGCCCCGGAAGGGGTCCCAGAAGAGGCCTCCTTCTACTATGGAACC  
TTCCCTCTTGCTTCTCCTGGGGCGTGGGCAGTTCCTGCCTACCAGACGGAGGGCGCCTGG  
GACCAGGACGGGAAAGGGCCTAGCATCTGGGACGTCTTCACACACAGTGGGAAGGGGAAA  
GTGCTTGGGAATGAGACGGCAGATGTAGCCTGTGACGGCTACTACAAGGTCCAGGAGGAC  
ATCATTCTGCTGAGGGAACTGCACGTCAACCACTACCGATTCTCCCTGTCTTGGCCCCGG  
CTCCTGCCACAGGCATCCGAGCCGAGCAGGTGAACAAGAAGGGAATCGAATTCTACAGT  
GATCTTATCGATGCCCTTCTGAGCAGCAACATCACTCCCATCGTGACCTTGCACTACTGG  
GATCTGCCACAGCTGCTCCAGGTCAAATACGGTGGGTGGCAGAATGTGAGCATGGCCAAC  
TACTTCAGAGACTACGCCAACCTGTGCTTTGAGGCCTTTGGGGACCGTGTGAAGCACTGG  
ATCACGTTCAGTGATCCTCGGGCAATGGCAGAAAAAGGCTATGAGACGGGGCCACCATGCG  
CCGGGCCTGAAGCTCCGCGGCACCGGCCTGTACAAGGCAGCACACCACATCATTAAGGCC  
CACGCCAAAACCTGGCATTCTTATAACACCACGTGGCGCAGCAAGCAGCAAGGTCTGGTG  
GGAATTTCACTGAACTGTGACTGGGGGGAACCTGTGGACATTAGTAACCCCAAGGACCTA  
GAGGCTGCCGAGAGATACCTACAGTTCTGTCTGGGCTGGTTTGCCAACCCCATTTATGCC  
GGTGACTACCCCAAGTCATGAAGGACTACATTGGAAGAAAGAGTGCAGAGCAAGGCCTG  
GAGATGTCGAGGTTACCGGTGTTCTCACTCCAGGAGAAGAGCTACATTAAAGGCACATCC  
GATTTCTTGGGATTAGGTCATTTTACTACTCGGTACATCACGGAAGGAACTACCCCTCC  
CGCCAGGGGGCCAGCTACCAGAACGATCGTGACTTGATAGAGCTGGTTGACCCAAACTGG  
CCAGATCTGGGGTCTAAATGGCTATATTCTGTGCCATGGGGATTAGGAGGCTCCTTAAC  
TTTGCTCAGACTCAATACGGTGATCCTCCCATATATGTGATGGAAAATGGAGCATCTCAA  
AAATTCCACTGTACTCAATTATGTGATGAGTGGAGAATTCAATACCTTAAAGGATACATA  
AATGAAATGCTAAAAGCTATAAAAGATGGTGCTAATATAAAGGGGTATACTTCCTGGTCT  
CTGTTGGATAAGTTTGAATGGGAGAAAGGATACTCAGATAGATATGGATTCTACTATGTT  
GAATTTAACGACAGAAATAAGCCTCGCTATCCAAAGGCTTCAGTTCAATATTACAAGAAG  
ATTATCATTGCCAATGGGTTTCCCAATCCAAGAGAGGTGGAAAGTTGGTACCTCAAAGCT  
TTGGAAACTTGCTCTATCAACAATCAGATGCTTGCTGCAGAGCCTTTGCTAAGTCACATG  
CAAATGGTTACGGAGATCGTGGTACCCACTGTCTGCTCCCTCTGTGCTCCTCATCACTGCT  
GTTCTACTAATGCTCCTCCTGAGGAGGCAGAGCTTGAGACAGGATTATCAATTTTGGAGCT  
TCATAAGAGAATCTTCAGGATCTTCCTCCCTTTTCTGCTTTGAGGGTTTCCATACATTGC  
TGTTTTTCAGGTTCTACAATAATTACCTTTTTTTCTCTTTCTCTTTTGGCTTGTGCTGGG  
ATTTAAGAATTAGAAAATAAAAATAAGCAGAAATTA

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**FIGURE 348**

MKPVVWVATLLWMLLLVPRLGAARKGSPEEASFYYGTFPLGFSWGVGSSAYQTEGAWDQDG  
KGPSIWDVFTHSKGKVLGNETADVACDGYKQVEDIILLRELHVNHYRFSLSWPRLLP  
GIRAEQVNKKGIEFYSDLIDALLSSNITPIVTLHHWDLPQLLQVKYGGWQNVSMANYFRD  
YANLCFEAFGDRVKHWITFSDPRAMAEGYETGHHAPGLKLRGTGLYKAAHHIIKAHAKT  
WHSYNTTWRSKQQGLVGISLNCDWGEPVDISNPKDLEAAERYLQFCLGWFANPIYAGDYP  
QVMKDYIGRKSAREQGLEMSRLPVFSLQEKSYIKGTSDFLGLGHFTTRYITERNYPSRQGP  
SYQNDRLIELVDPNWPDLGSKWLYSVPWGFRRLLNFAQTQYGDPIYVMENGASQKFHC  
TQLCDEWRIQYLKGYINEMLKAIKDGANIKGYTSWSLLDKFEWEKGYSDRYGFYYVEFND  
RNKPRYPKASVQYYKKIIANGFPNPREVESWYLKALETCSINNQMLAAEPLLSHMQMVT  
EIVVPTVCSLCVLITAVLLMLLLRRQS

**Important features:****Signal peptide:**

amino acids 1-21

**Transmembrane domain:**

amino acids 541-558

**N-glycosylation sites:**

amino acids 80-84, 171-175, 245-249

**Glycosaminoglycan attachment site:**

amino acids 72-76

**cAMP- and cGMP-dependent protein kinase phosphorylation sites:**

amino acids 23-27, 564-568

**Tyrosine kinase phosphorylation sites:**

amino acids 203-211, 347-355, 460-468, 507-514

**N-myristoylation sites:**

amino acids 44-50, 79-85, 167-173, 225-231, 257-263, 315-321

**Amidation site:**

amino acids 307-311

**Glycosyl hydrolases family 1 active site:**

amino acids 407-416

**Glycosyl hydrolases family 1 N-terminal signature:**

amino acids 41-56

**Motif name Glycosyl hydrolases family:**

amino acids 37- 67

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**FIGURE 349**

CGCAAAGCCGCCCTCGGGGCGCTCATGGCGGGACGCCTCCTGGGAAAGGCTTTAGCCGCG  
GTGTCTCTCTCTCTGGCCTTGGCCTCTGTGACTATCAGGTCCTCGCGCTGCCGCGGCATC  
CAGGCGTTTCAGAACTCGTTTTTCATCTTCTTGGTTTTTCATCTTAATACCAACGTCATGTCT  
GGTTCTAATGGTTCCAAAGAAAATTCTCACATAAGGCTCGGACGTCTCCTTACCCAGGT  
TCAAAAGTTGAACGAAGCCAGGTTCTAATGAGAAAGTGGGCTGGCTTGTTGAGTGGCAA  
GACTATAAGCCTGTGGAATACACTGCAGTCTCTGTCTTGGCTGGACCCAGGTGGGCAGAT  
CCTCAGATCAGTGAAAGTAATTTTTCTCCCAAGTTTAACGAAAAGGATGGGCATGTTGAG  
AGAAAGAGCAAGAATGGCCTGTATGAGATTGAAAATGGAAGACCGAGAAATCCTGCAGGA  
CGGACTGGACTGGTGGGCCGGGGGCTTTTGGGGCGATGGGGCCCAAATCACGCTGCAGAT  
CCCATTATAACCAGATGGAAAAGGGATAGCAGTGGAAATAAAATCATGCATCCTGTTTTCT  
GGGAAGCATATCTTACAATTTGTTGCAATAAAAAGGAAAGACTGTGGAGAATGGGCAATC  
CCAGGGGGGATGGTGGATCCAGGAGAGAAGATTAGTGCCCACTGAAAAGAGAATTTGGT  
GAGGAAGCTCTCAACTCCTTACAGAAAACCAGTGCTGAGAAGAGAGAAATAGAGGAAAAG  
TTGCACAACTCTTCAGCCAAGACCACCTAGTGATATATAAGGGATATGTTGATGATCCT  
CGAAACACTGATAATGCATGGATGGAGACAGAAGCTGTGAACTACCATGACGAAACAGGT  
GAGATAATGGATAATCTTATGCTAGAAGCTGGAGATGATGCTGGAAAAGTGAAATGGGTG  
GACATCAATGATAAACTGAAGCTTTATGCCAGTCACTCTCAATTCATCAAACCTTGTGGCT  
GAGAAACGAGATGCACACTGGAGCGAGGACTCTGAAGCTGACTGCCATGCGTTGTAGCTG  
ATGGTCTCCGTGTAAGCCAAAGGCCACAGAGGAGCATATACTGAAAAGAAGGCAGTATC  
ACAGAATTTATACTATAAAAAGGGCAGGGTAGGCCACTTGGCCTATTTACTTTCAAAACA  
ATTTGCATTTAGAGTGTTTCGCATCAGAATAACATGAGTAAGATGAACTGGAACACAAAA  
TTTTTCAGCTCTTTGGTCAAAAGGAATATAAGTAATCATATTTTGTATGTATTCGATTTAA  
GCATGGCTTAAATTAAATTTAAACAATAATGCTCTTTGAAGAATCATAATCAGAATAAA  
GATAAATTCTTGATCAGCTATA

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**FIGURE 350**

MAGRLLGKALAAVSLSLALASVTIRSSRCRGIQAFRNSFSSSWFHLNTNVMMSGNNGSKEN  
SHNKARTSPYPGSKVERSQVPNEKVGWLVWQDYKPVEYTAVSVLAGPRWADPQISESNF  
SPKFNEKDGHVERKSKNGLYEIENGRPRNPAGRTGLVGRGLLGRWGNHAADPIITRWKR  
DSSGNKIMHPVSGKHILQFVAIKRKDCGEWAI PGGMVDPGEKISATLKREFGEEALNSLQ  
KTSAEKREIEEKLHKLFSQDHLVIYKGYVDDPRNTDNAWMETEAVNYHDETGEIMDNLM  
EAGDDAGKVKWVDINDKLKLYASHSQFIKLVAEKRDAHWSSEADCHAL

**Important features of the protein:****Signal peptide:**

1-20

**Transmembrane domain:**

None

**N-glycosylation site:**

55-59

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

179-183

**N-myristoylation site:**

53-59, 56-62

**mutT domain signature:**

215-235

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**FIGURE 351**

CCTCTGTCTGTGCTCCCATCCCAGGGAGTATAGGTGGAGCCTCCAGAGCCCATGGACAGG  
GCATGCTGGGGCTGGGCCAGCCCCAGCGGTGTCTCTAAGGCACCCCTGGGATCCCCACTG  
AGCTGGCCTACTTCAGACAGCCAGGGCCCCACCCCTCTGGCCCCCTTAGTGTCCAGCTCGT  
GGCCCCCTTGGCATTTCCACAAGACGCCAAGATGGAGATTCCCATGGGGACCCAGGGCTGC  
TTCTCAAAGAGCCTCCTGCTCTCAGCCTCAATCCTGGTCCTCTGGATGCTCCAAGGCTCC  
CAGGCAGCTCTCTACATCCAGAAGATTCCAGAGCAGCCTCAAAAGAACCAGGACCTTCTC  
CTGTCAGTCCAGGGTGTCCAGACACCTTCCAGGACTTCAACTGGTACCTGGGGGAGGAG  
ACGTACGGAGGCACGAGGCTATTTACCTACATCCCTGGGATACAACGGCCTCAGAGGGAT  
GGCAGTGCCATGGGACAGCGAGACATCGTGGGCTTCCCCAATGGTTCCATGCTGCTGCGC  
CGCGCCCAGCCTACAGACAGTGGCACCTACCAAGTAGCCATTACCATCAACTCTGAATGG  
ACTATGAAGGCCAAGACTGAGGTCCAGGTAGCTGAAAAGAATAAGGAGCTGCCCAGTACA  
CACCTGCCCCACCAACGCTGGGATCCTGGCGGCCACCATCATTTGGATCTCTTGCTGCCGGG  
GCCCTTCTCATCAGCTGCATTGCCATCTCTCTGGTGACAAGGAACTGGAGGGGCCAGAGC  
CACAGACTGCCTGCTCCGAGGGGCCAGGGATCTCTGTCCATCTTGTGCTCGGCTGTATCC  
CCAGTGCCTTCAGTGACGCCCAGCACATGGATGGCGACCACAGAGAAGCCAGAATTGGGC  
CCTGCTCATGATGCTGGTGACAACAACATCTATGAAGTGATGCCCTCTCCAGTCTCTCTG  
GTGTCCCCCATCAGTGACACAAGGTCCATAAACCCAGCCCGGCCCTTGCCACACCCCCA  
CACCTGCAGGCGGAGCCAGAGAACCACCAGTACCAGCAGGACCTGCTAAACCCCGACCCT  
GCCCCCTACTGCCAGCTGGTGCCAACTTCCTGATGGGTCTTGGGCCAGGCCAGCCAGGGA  
GAAGACAAGGCCCCAGCCCTCCTCTGGGAGCCTCACACCTGAGACCAGCAGGACAAGGCC  
ATTGGGGGCTGTGGGGCCGATGAGGTGGACTCAGCCAAAGACTCAGCAGCACATGGGGCA  
GGTGTCTTGGCAGGGGGACAGGAGACTGTAACAGGCCCCAGGTCTTGTGCAGCCCCTGAA  
TGCACGCCCCGCTTTCGGTCTGTTCTTCAAGCAAGCTGGCCTGGGCCATGTGCCTGTGAA  
AGGCAGGCTCTGGCCCCCTTTCCATGCCAAAGTCCCCCAAGATCTGGATATCTGGGGACAA  
GATGGTGGCCTCAGGCCTGCCTCCCAGGCAGTTGGCTGGGCTCCCAACTGTCTGTCTCTCA  
ATGCCCTACCCCCAACTCCACTAGTGACCCTCAGAGTCTTCTCCCCTTAGGACAAGGCAGA  
CACCCCACCATGCGGGCCTCAGGTGGCAGAGAGGCCAGCCTCACAGGCCTGTGGCCCCA  
CACACCAGTCCCAGCAAGGTGACCACGGCTGCTGGACCCCTTCCCTGTTTCAGGCAGGCCC  
AGCCCCCTCTCAGAACCTGCTGCCAGCTGCTGGTCTTGGCCCCCACCCCTGAATCTTACTGA  
GTCCCTCTGGGCAGCAGCTCCCTTCTCCACCCCACCCAGCACCCGTCCCAAATGTGGCC  
TCAGCTTGTCCTCCCCTTCCCCAACTATGCATTCAATTCAGCAATAAATGAGCCTTTGCT  
GCA

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**FIGURE 352**

MEIPMGQTQGCFSKSLLLSASILVLWMLQGSQAALYIQKIPEQPQKNQDLLLSVQGVPDF  
QDFNWYLGEETYGGTRLFTYIPGIQRPQRDGSAMGQRDIVGFPNGSMLLRRAQPTDSGTY  
QVAITINSEWTMKAKTEVQVAEKNKELPSTHLPTNAGILAATIIGSLAAGALLISCIAYL  
LVTRNWRGQSHRLPAPRGQGSLSILCSAVSPVPSVTPSTWMATTEKPELGPAGDAGDNNI  
YEVMPSPVLLVSPISDTRSINPARPLPTPHLQAEPENHQYQQDLLNPDAPYQCQLVPTS

**Important features of the protein:****Signal peptide:**

Amino acids 1-32

**Transmembrane domain:**

Amino acids 159-178

**N-glycosylation site:**

Amino acids 104-108

**N-myristoylation sites:**

Amino acids 6-12; 29-35; 55-61; 91-97; 157-163; 165-171



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**FIGURE 353**

CTTCAGAACAGGTTCTCCTTCCCCAGTCACCAGTTGCTCGAGTTAGAATTGTCTGCAATG  
GCCGCCCTGCAGAAATCTGTGAGCTCTTTCCTTATGGGGACCCTGGCCACCAGCTGCCTC  
CTTCTCTTGGCCCTCTTGGTACAGGGAGGAGCAGCTGCGCCCATCAGCTCCCACTGCAGG  
CTTGACAAGTCCAACTTCCAGCAGCCCTATATCACCAACCGCACCTTCATGCTGGCTAAG  
GAGGCTAGCTTGGCTGATAACAACACAGACGTTTCGTCTCATTGGGGAGAACTGTTCCAC  
GGAGTCAGTATGAGTGAGCGCTGCTATCTGATGAAGCAGGTGCTGAAC TTCACCCTTGAA  
GAAGTGCTGTTCCCTCAATCTGATAGGTTCCAGCCTTATATGCAGGAGGTGGTGGCCCTTC  
CTGGCCAGGCTCAGCAACAGGCTAAGCACATGTCATATTGAAGGTGATGACCTGCATATC  
CAGAGGAATGTGCAAAAGCTGAAGGACACAGTGAAAAAGCTTGGAGAGAGTGAGAGATC  
AAAGCAATTGGAGAACTGGATTTGCTGTTTATGTCTCTGAGAAATGCCTGCATTTGACCA  
GAGCAAAGCTGAAAAATGAATAACTAACCCCTTTCCTGCTAGAAATAACAATTAGATG  
CCCCAAAGCGATTTTTTTTAACCAAAAGGAAGATGGGAAGCCAACTCCATCATGATGGG  
TGGATTCCAAATGAACCCCTGCGTTAGTTACAAAGGAAACCAATGCCACTTTTGTTTATA  
AGACCAGAAGGTAGACTTTCTAAGCATAGATATTTATTGATAACATTTTCATTGTAAGTGG  
TGTTCTATACACAGAAAACAATTTATTTTTTAAATAATTGTCTTTTCCATAAAAAAGAT  
TACTTTCCATTCCCTTAGGGGAAAAAACCCCTAAATAGCTTCATGTTTCCATAATCAGTA  
CTTTATATTTATAAATGTATTTATTATTATTATAAGACTGCATTTTATTTATATCATTTT  
ATTAATATGGATTTATTTATAGAAACATCATTCGATATTGCTACTTGAGTGTAAGGCTAA  
TATTGATATTTATGACAATAATTATAGAGCTATAACATGTTTATTTGACCTCAATAAACA  
CTTGGATATCCC

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**FIGURE 354**

MAALQKSVSSFLMGTLATSCLLLLLALLVQGGAAAPISSHCRLDKSNFQQPYITNRTFMLA  
KEASLADNNTDVRLIGEKLFHGVSMSERCYLMKQVLNFTLEEVLFPQSDRFQPYMQEVVP  
FLARLSNRLSTCHIEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACI

**Important features of the protein:**

**Signal peptide:**

amino acids 1-33

**N-glycosylation sites:**

amino acids 54-58, 68-72, 97-101

**N-myristoylation sites:**

amino acids 14-20, 82-88

**Prokaryotic membrane lipoprotein lipid attachment site:**

amino acids 10-21

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**FIGURE 355**

TGGCCTACTGGAAAAAAAAAAAAAAAAAAAAAGTCACCCGGGCCCCGCGGTGGCCACAA  
CATGGCTGCGGCGCCGGGGCTGCTCTTCTGGCTGTTTCGTGCTGGGGGCGCTCTGGTGGGT  
CCCGGGCCAGTCGGATCTCAGCCACGGACGGCGTTTCTCGGACCTCAAAGTGTGCGGGGA  
CGAAGAGTGCAGCATGTTAATGTACCGTGGGAAAGCTCTTGAAGACTTCACGGGCCCTGA  
TTGTCGTTTTGTGAATTTTAAAAAAGGTGACGATGTATATGTCTACTACAAACTGGCAGG  
GGGATCCCTTGAACCTTTGGGCTGGAAGTGTTGAACACAGTTTTGGATATTTTCCAAAAGA  
TTTGATCAAGGTACTTCATAAATACACGGAAGAAGAGCTACATATTCCAGCAGATGAGAC  
AGACTTTGTCTGCTTTGAAGGAGGAAGAGATGATTTTAATAGTTATAATGTAGAAGAGCT  
TTTAGGATCTTTGGAACCTGGAGGACTCTGTACCTGAAGAGTCGAAGAAAGCTGAAGAAGT  
TTCTCAGCACAGAGAGAAATCTCCTGAGGAGTCTCGGGGGCGTGAACTTGACCCTGTGCC  
TGAGCCCGAGGCATTTCAGAGCTGATTTCAGAGGATGGAGAAGGTGCTTTCTCAGAGAGCAC  
CGAGGGGCTGCAGGGACAGCCCTCAGCTCAGGAGAGCCACCCTCACACCAGCGGTCTTGC  
GGCTAACGCTCAGGGAGTGCAGTCTTCGTTGGACACTTTTGAAGAAATTCTGCACGATAA  
ATTGAAAGTGCCGGGAAGCGAAAGCAGAACTGGCAATAGTTCTCCTGCCTCGGTGGAGCG  
GGAGAAGACAGATGCTTACAAAGTCCTGAAAACAGAAATGAGTCAGAGAGGAAGTGGACA  
GTGCGTTATTATTACAGCAAAGGATTTTCGTTGGCATCAAAATCTAAGTTTGTTTTACAA  
AGATTGTTTTTAGTACTAAGCTGCCTTGGCAGTTTGCATTTTGTAGCCAAACAAAAATAT  
ATTATTTTCCCTTCTAAGTAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 356**

MAAAPGLLFWLFLVGLALWWVPGQSDLSHGRRFSDLKVCGDEECSSMLMYRGKALEDFTGPD  
CRFVNFKKGDDVYVYYKLAGGSLELWAGSVEHSFGYFPKDLIKVLHKEYTEELHIPADET  
DFVCFEGGRDDFNSYNVEELLGSLELEDSVPEESKKAEEVSQHREKSPPEESRGRELDVPV  
EPEAFRADSEEDGEGAFSESTEGGLQGQPSAQESHPTSGPAANAQGVQSSLDTFEEILHDK  
LKVPGESERTGNSSPASVEREKTDAYKVLKTEMSQRGSGQCVIHYSKGFRWHQNLSLFYK  
DCF

**Important features of the protein:**

**Signal peptide:**

amino acids 1-22

**N-glycosylation site:**

amino acids 294-298

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 30-34

**Tyrosine kinase phosphorylation site:**

amino acids 67-76

**N-myristoylation sites:**

amino acids 205-211, 225-231, 277-283

**Amidation site:**

amino acids 28-32

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**FIGURE 357**

ACGCGCCCCGGCAGCTGTCCACCGATCCCGGCCACCGCCCCCGGCCACCCCCACCCCCGCGA  
GCCCCATGGAGGCTCCGGGACCCCGCGCCTTGCGGACTGCGCTCTGTGGCGGCTGTTGCTG  
CCTCCTCCTATGTGCCAGCTGGCTGTGGCTGGTAAAGGAGCTCGAGGCTTTGGGAGGGG  
AGCCCTGATCCGCCTGAATATCTGGCCGGCGGTCCAAGGGGCCTGCAAACAGCTGGAGGT  
CTGTGAGCACTGCGTGAGGGAGACAGAGCGCGCAATCTCTCAGCTGCATGTGGGAGCA  
GTGCCGGCCAGAGGAGCCAGGACACTGTGTGGCCCAATCTGAGGTGGTCAAGGAAGGTTG  
CTCCATCTACAACCGCTCAGAGGCATGTCCAGCTGCTCACCACCACCCCACCTATGAACC  
GAAGACAGTCACAACAGGGAGCCCCCAGTCCCTGAGGCCACAGCCCTGGATTGTACGG  
GGCCAGCTTTATCGGAGGTGTCGTGCTGGTGTGAGCCTACAGGCGGTGGCTTTCTTTGT  
GCTGCACTTCTCAAGGCCAAGGACAGCACCTACCAGACGCTGTGAGTACCTGGCCAGCA  
GCAAGTACCTGAGTCCAGCTCACCTCCTGGTTCCTGCCCCACCGTTCCCTTCAGTACC  
CAGGGTGCTGTCTTCTCCATGGGCAAGCCCTCAGGACGGTGACAGCGTGCTCCATGTGAG  
CCACACCCTTTTGTCTCCTCCAGTTGGGGTGTTTCCTTTGTGAGATGTTGGCTGGGACC  
AGGACTCAGCCTGGGCCAGTCTAGGAGGCCAGCTGAGCCCTCCTGTGTCTTTTCCCTTCA  
TGCTGCCAGCAGGGAAGAGAACCAGTAGGTGCCAGCCAGGCAAGCCTGTGGCCCGCGTT  
TCTGTGGCTGTGGGCAGGAGCTGGGCCTTGTTCTAGTTGGGTTTTGCTCTGAGAAGGGG  
AGCTGTGCCTGAGGCCCTCTGTGTGCCGTGTGTGCTGTGGGGCGGGTCGCCACAGCCTGT  
GTTAAAGTGTTTGCTCTTCCTCTGCTGCCTCCTCTCGAGGCAGGGGGTCCTTGCTGGCT  
GAGGCAGTGTACCTTCCTGAGTGTCTCTTTGGCCTCTGCAGAATCTGACCCCTTTGGG  
CCTGGACTCCATCCTGAGGGGAAAGGAGGATGCAGAGGGTGGCCTCTGGGCACCCCTTG  
GGTAAGCGGGGGGCGGGGGCGGGAAAAA

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**FIGURE 358**

MEAPGPRLRTALCGGCCLLLLCAQLAVAGKGARGFGRGALIRLNIWPAVQGACKQLEVC  
EHCVEGDRARNLSSCMWEQCRPEEPGHCVAQSEVVKEGCSIYNRSEACPAHHHPTYPEPK  
TVTTGSPPVPEAHSPGFDGASFIGGVVLVLSLQAVAFFVLHFLKAKDSTYQTL

**Important features of the protein:**

**Signal peptide:**

1-29

**Transmembrane domain:**

141-160

**N-glycosylation site:**

71-75, 103-107

**Tyrosine kinase phosphorylation site:**

164-171

**N-myristoylation site:**

15-21

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**FIGURE 359**

TTCCAGTCAGAGTTAAGTTAAACAGAAAAAGGAAGATGGCAAGAATATTGTTACTTTT  
CCTCCCGGGTCTTGTGGCTGTATGTGCTGTGCATGGAATATTTATGGACCGTCTAGCTTC  
CAAGAAGCTCTGTGCAGATGATGAGTGTGTCTATACTATTTCTCTGGCTAGTGCTCAAGA  
AGATTATAATGCCCCGGACTGTAGATTCATTAACGTTAAAAAAGGGCAGCAGATCTATGT  
GTA<sup>1</sup>CTCAAAGCTGGTAAAAGAAAATGGAGCTGGAGAATTTTGGGCTGGCAGTGTTTATGG  
TGATGGCCAGGACGAGATGGGAGTCGTGGGTATTTCCCCAGGAACCTGGTCAAGGAACA  
GCGTGTGTACCAGGAAGCTACCAAGGAAGTTCCCACCACGGATATTGACTTCTTCTGCGA  
GTAATAAATTAGTTAA<sup>2</sup>AACTGCAAATAGAAAGAAAACACCAAAAATAAAGAAAAGAGCAA  
AAGTGGCCAAAAAATGCATGTCTGTAATTTTGGACTGACGT

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## FIGURE 360

MARILLFLPGLVAVCAVHGIFMDRLASKKLCADDECVTISLASAQEDYNAPDCRFINV  
KKGQQIYVYSKLVKENGAGEFWAGSVYGDGQDEMGVVGYPFRNLVKEQRVYQEATKEVPT  
TDIDFFCE

Important features of the protein:

Signal peptide:  
1-14

Transmembrane domain:  
None

N-myristoylation site:  
84-90



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**FIGURE 361**

GGCACGAGCCACCACTTACAACCACACAGCCTATCCAGAAACATGAAGATAAGAAATGCT  
TGTGCTGTCCCTTATTGAAGTACTCCTGTTTATACTTGAAGGAGTTACAGGAGCTCGAAAA  
ATTTCAACTTTCTCAGGCCCTGGCTCATGGCCGTGCAATCCCAAGTGTGATGGCAGAAGT  
TACAACCCCTCAGAGGAGTGTGTGTTTCATGACACCATCCTGCCCTTTAAGCGGATTAAC  
CTCTGTGGCCCTAGCTGCACCTACAGGCCCTGCTTTGAGCTCTGCTGTCTGAGTCCTAT  
AGCCCCAAGAAGAAATTTATTGTCAAGCTTAAAGTTCATGGAGAGAGATCCCATTGCAGT  
TCATCCCCTATCTCCAGGAAGTGTAAAAGCAACAAGATTTTTTCATGGAGAAGATATTGAA  
GACAACCAACTTTCTCTTAGGAAAAAAAGTGGTGACCAGCCTTGAGAGTCTGCTTTCTTC  
CTGCAAGCACCAGTTCCTGAATGTTCTTACTTGAAGAATGGATACCTGAAGCATTGGGGT  
GCAGTGATATATGTGTCTCATTACAATGCTCCTTTGGATATTGTTTTCTTAAGCATGTGT  
TGGAATGTTCCCCCATAACTTTCTAAAATTATCCTATTTCAATGCAACTAAAGATAAATG  
TATTCAGCCAGAGTCCACAGAGAAGGCAAGTTATGCAAGGCAGGCATGGGGCCCTCACA  
AAATTTCAAGCTGTGCGACTTATGTAGTAATTTTCTACAAACAATCCCTCCTGGATATCC  
AGGAGGCTCCAGACCTGAATAAAAACCACATGTCTGTCTAGAAAAAGGGAATGAATCAAG  
ATCCACAGGACCTTTTCAAGATTTTAGAAGCAGCAAACTATGGCTGAGAGAAAAGACTCT  
CTGACCAGGCAAATTGTTCTGCAGTATTCTCGGGCGTGTAGCTCCCCTGAGTAGTCGCC  
AGGCTGGTCTTGGCTTTGTAATAATACAGCTGCCTTTGAGTCCTCCCTACCCTGTTAGTA  
ACCCCTTGCCTGCACTGTTGTCCTTACAACCGAAATAAACTGATTAGTTG

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**FIGURE 362**

MKIRNACAVLIEVLLFILEGVTGARKISTFSGPGSWPCNPKCDGRTYNPSEECCVHDTIL  
PFKRINLCGPSCTYRPCFELCCPESYSPKKKFIVKLKVHGERSHCSSSPISRNCKSNKIF  
HGEDIEDNQLSLRKKSGDQP

**Important features of the protein:**

**Signal peptide:**

1-23

**Transmembrane domain:**

None

**Glycosaminoglycan attachment site:**

31-35

**N-myristoylation site:**

20-26, 34-40

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**FIGURE 363**

ACACTGGCCAAACAAAAACGAAAGCACTCCGTGCTGGAAGTAGGAGGAGAGTCAGGACTC  
CCAGGACAGAGAGTGCACAACTACCCAGCACAGCCCCCTCCGCCCCCTCTGGAGGCTGA  
AGAGGGATTCAGCCCCCTGCCACCCACAGACACGGGCTGACTGGGGTGTCTGCCCCCTT  
GGGGGGGGGAGCAGCACAGGGCCTCAGGCCTGGGTGCCACCTGGCACCTAGAAGATGCCTGT  
GCCCTGGTTCTTGCTGTCTTGGCACTGGGCCGAAGCCCAGTGGTCCTTTCTCTGGAGAG  
GCTTGTGGGGCCTCAGGACGCTACCCACTGCTCTCCGGGCCTCTCCTGCCGCCTCTGGGA  
CAGTGACATACTCTGCCTGCCTGGGGACATCGTGCCTGCTCCGGGCCCCGTGCTGGCGCC  
TACGCACCTGCAGACAGAGCTGGTGCTGAGGTGCCAGAAGGAGACCGACTGTGACCTCTG  
TCTGCGTGTGGCTGTCCACTTGGCCGTGCATGGGCACTGGGAAGAGCCTGAAGATGAGGA  
AAAGTTTGGAGGAGCAGCTGACTCAGGGGTGGAGGAGCCTAGGAATGCCTCTCTCCAGGC  
CCAAGTCGTGCTCTCCTTCCAGGCCTACCCACTGCCCCGCTGCGTCTTGCTGGAGGTGCA  
AGTGCTGCTGCCCTTGTGCAGTTTGGTCAGTCTGTGGGCTCTGTGGTATATGACTGCTT  
CGAGGCTGCCCTAGGGAGTGAGGTACGAATCTGGTCTATACTCAGCCCAGGTACGAGAA  
GGAACCTCAACCACACACAGCAGCTGCCTGCCCTGCCCTGGCTCAACGTGTCAGCAGATGG  
TGACAACGTGCATCTGGTTCTGAATGTCTCTGAGGAGCAGCACTTCGGCCTCTCCCTGTA  
CTGGAATCAGGTCCAGGGCCCCCCTAAACCCCGGTGGCACAAAAACCTGACTGGACCGCA  
GATCATTACCTTGAACCACACAGACCTGGTTCCCTGCCTCTGTATTAGGTGTGGCCTCT  
GGAACCTGACTCCGTTAGGACGAACATCTGCCCCCTCAGGGAGGACCCCCGCGCACACCA  
GAACCTCTGGCAAGCCGCCCCGACTGCGACTGCTGACCCTGCAGAGCTGGCTGCTGGACGC  
ACCGTGCTCGCTGCCCGCAGAAGCGGCACTGTGCTGGCGGGCTCCGGGTGGGGACCCCTG  
CCAGCCACTGGTCCCACCGCTTTCTGGGAGAACGTCACTGTGGACAAGGTTCTCGAGTT  
CCCATTGCTGAAAGGCCACCCTAACCTCTGTGTTAGGTGAACAGCTCGGAGAAGCTGCA  
GCTGCAGGAGTGCTTGTGGGCTGACTCCCTGGGGCCTCTCAAAGACGATGTGCTACTGTT  
GGAGACACGAGGCCCCCAGGACAACAGATCCCTCTGTGCCTTGAACCCAGTGGCTGTAC  
TTCACTACCCAGCAAAGCCTCCACGAGGGCAGCTCGCCTTGGAGAGTACTTACTACAAGA  
CCTGCAGTCAGGCCAGTGTCTGCAGCTATGGGACGATGACTTGGGAGCGCTATGGGCCTG  
CCCCATGGACAAATACATCCACAAGCGCTGGGCCCTCGTGTGGCTGGCCTGCCTACTCTT  
TGCCGCTGCGCTTTCCCTCATCCTCCTTCTCAAAAAGGATCACGCGAAAGGGTGGCTGAG  
GCTCTTGAAACAGGACGTCCGCTCGGGGGCGGCCCGCCAGGGGCCGCGCGGCTCTGCTCCT  
CTACTCAGCCGATGACTCGGGTTTCGAGCGCCTGGTGGGCGCCCTGGCGTCCGCCCTGTG  
CCAGCTGCCGCTGCGCGTGGCCGTAGACCTGTGGAGCCGTCTGTAAGTGAAGCGCGCAGGG  
GCCCCGTGGCTTGGTTTCACGCGCAGCGGCCAGACCCTGCAGGAGGGCGGCGTGGTGGT  
CTTGCTCTTCTCTCCCGGTGCGGTGGCGCTGTGCAGCGAGTGGCTACAGGATGGGGTGTC  
CGGGCCCCGGGGCGCACGGCCCCGCACGACGCCTTCCGCGCCTCGCTCAGCTGCGTGCTGCC  
CGACTTCTTGCAAGGCCGGGCGCCCGGCAGCTACGTGGGGGCTGCTTCGACAGGCTGCT  
CCACCCGACGCCGTACCCGCCCTTTTCCGCACCGTGCCCGTCTTCACTGCCCCTCCA  
ACTGCCAGACTTCTGGGGGCCCTGCAGCAGCCTCGCGCCCCGCGTTCGGGGCGGCTCCA  
AGAGAGAGCGGAGCAAGTGTCCCGGGCCCTTCAAGCCAGCCCTGGATAGCTACTTCCATCC  
CCCGGGGACTCCCGCGCCGGGACGCGGGGTGGGACCAGGGCGGGACCTGGGGCGGGGGA  
CGGGACTTAAATAAAGGCAGACGCTGTTTTTCTAAAAAA

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**FIGURE 364**

MPVPWFLLSLALGRSPVVLSELERLVGPQDATHCSPGLSCRLWDS DILCLPGDIVPAPGPV  
LAPTHLQTELVLRCQKETDCDLCLRVAVHLAVHGHWEPEDEEKFGGAADSGVEEPRNAS  
LQAQVVL SFQAYPTARCVLLEVQVPAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPR  
YEKELNHTQQLPALPWLNV SADGDNVHLVLNVSEEQHFGLSLYWNQVQGP PKPRWHKNLT  
GPQIITLNHTDLVPCLCIQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLTLQSWL  
LDAPCSLPAAEALCWRAPGGDPCQPLVPPLSWENVTVDKVLEFP LLKGHPNLCVQVNSSE  
KLQLQECLWADSLGPLKDDVLLLETRGPQDNRS LCALEPSGCTSLPSKASTRAARLGEYL  
LQDLQSGQCLQLWDDDLGALWACPMKYIHKRWALVWLACLLFAAALSLILLLKKDHAKG  
WLRLLLKQDVRS GAAARGRAALLLYSADDSGFERLVGALASALCQLPLRVAVDLWSRRELS  
AQGPVAFWFAQRRTLQEGGVVLLFSPGAVALCSEWLQDGVSGPGAHGPHDAFRASLSC  
VLPDFLQGRAPGSYVGACFDRL LHPDAVPALFRTVPVFTLPSQLPDLGALQQPRAPRSG  
RLQERAEQVSRALQPALDSYFHPPGTPAPGRGVGPGAGPGAGDGT

**Signal sequence:**

amino acids 1-20

**Transmembrane domain:**

amino acids 453-475

**N-glycosylation sites:**amino acids 118-121, 186-189, 198-201, 211-214, 238-241,  
248-251, 334-337, 357-360, 391-394**Glycosaminoglycan attachment site:**

amino acids 583-586

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

amino acids 552-555

**N-myristoylation sites:**amino acids 107-112, 152-157, 319-324, 438-443, 516-521,  
612-617, 692-697, 696-701, 700-705

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**FIGURE 365**

AATAGAAGTCCTCAGGACGGAGCAGAGGTGGCCGGCGGGCCCGGCTGACTGCGCCTCTGC  
TTTCTTTCCATAACCTTTTCTTTCGGAATCGAATCACGGCTGCTGCGAAGGGTCTAGTTC  
CGGACACTAGGGTGCCCGAACGCGCTGATGCCCCGAGTGCTCGCAGGGCTTCCCGCTAAC  
CATGCTGCCGCCGCCGCGGCCCGCAGCTGCCTTGGCGCTGCCTGTGCTCCTGCTACTGCT  
GGTGGTGCTGACGCCGCCCCGACCGGCGCAAGGCCATCCCCAGGCCCAGATTACCTGCG  
GCGCGGCTGGATGCGGCTGCTAGCGGAGGGCGAGGGCTGCGCTCCCTGCCGGCCAGAAGA  
GTGCGCCGCGCCGCGGGGCTGCCTGGCGGGCAGGGTGCGCGACGCGTGCGGCTGCTGCTG  
GGAATGCGCCAACCTCGAGGGCCAGCTCTGCGACCTGGACCCAGTGCTCACTTCTACGG  
GCACTGCGGCGAGCAGCTTGAGTGCCGGCTGGACACAGGCGGCGACCTGAGCCGCGGAGA  
GGTGCCGGAACCTCTGTGTGCCTGTGCTTCGAGAGTCCGCTCTGCGGGTCCGACGGTCA  
CACCTACTCCAGATCTGCCGCCTGCAGGAGGCGGCCCGCGCTCGGCCCGATGCCAACCT  
CACTGTGGCACACCCGGGGCCCTGCGAATCGGGGCCCCAGATCGTGTCACATCCATATGA  
CACTTGGAATGTGACAGGGCAGGATGTGATCTTTGGCTGTGAAGTGTTCCTACCCCAT  
GGCCTCCATCGAGTGGAGGAAGGATGGCTTGACATCCAGCTGCCAGGGGATGACCCCCA  
CATCTCTGTGCAGTTTAGGGGTGGACCCAGAGGTTTGAGGTGACTGGCTGGCTGCAGAT  
CCAGGCTGTGCGTCCAGTGATGAGGGCACTTACCGCTGCCTTGGCCGCAATGCCCTGGG  
TCAAGTGGAGGCCCCCTGCTAGCTTGACAGTGCTCACACCTGACCAGCTGAACTCTACAGG  
CATCCCCCAGCTGCGATCACTAAACCTGGTTCCCTGAGGAGGAGGCTGAGAGTGAAGAGAA  
TGACGATTACTACTAGGTCCAGAGCTCTGGCCCATGGGGGTGGGTGAGCGGCTATAGTGT  
TCATCCCTGCTCTTGAAAAGACCTGGAAAGGGGAGCAGGGTCCCTTCATCGACTGCTTTC  
ATGCTGTCAGTAGGGATGATCATGGGAGGCCTATTTGACTCCAAGGTAGCAGTGTGGTAG  
GATAGAGACAAAAGCTGGAGGAGGGTAGGGAGAGAAGCTGAGACCAGGACCGGTGGGGTA  
CAAAGGGGCCCATGCAGGAGATGCCCTGGCCAGTAGGACCTCCAACAGGTTGTTTCCCAG  
GCTGGGGTGGGGGCCTGAGCAGACACAGAGGTGCAGGCACCAGGATTCTCCACTTCTTCC  
AGCCCTGCTGGGCCACAGTTCTAACTGCCCTTCCCTCCAGGCCCTGGTTCTTGCTATTTC  
CTGGTCCCCAACGTTTATCTAGCTTGTTTGGCCCTTCCCCAAACTCATCTTCCAGAACTT  
TTCCCTCTCTCCTAAGCCCCAGTTGCACCTACTAACTGCAGTCCCTTTTGCTGTCTGCCG  
TCTTTTGTACAAGAGAGAGAACAGCGGAGCATGACTTAGTTCAGTGCAGAGAGATT

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**FIGURE 366**

MLPPPRPAAALALPVLLLLLVLTTPPPTGARPSPGPDYLRRGWMRLLAEGEGCAPCRPEE  
CAAPRGCLAGRVRDACGCCWECANLEGQLCDLDPSAHFYGHCGEQLECRDGTGGDLRGE  
VPEPLCACRSQSPLCGSDGHTYSQICRLQEAARARPDANLTVAHPGPCESGPQIVSHPYD  
TWNVTGQDVIFGCEVFAYPMASIEWRKDGLDIQLPGDDPHISVQFRGGPQRF EVTGWLQI  
QAVRPSDEGTYRCLGRNALGQVEAPASLTVLTPDQLNSTGIPQLRSLNLVPEEEAESEEN  
DDYY

**Important features of the protein:****Signal peptide:**

1-30

**Transmembrane domain:**

None

**N-glycosylation site:**

159-163, 183-187, 277-281

**Tyrosine kinase phosphorylation site:**

244-252

**N-myristoylation site:**

52-58, 66-72, 113-119, 249-255

**Kazal-type serine protease inhibitor domain:**

121-168

**Immunoglobulin domain:**

186-255

**Insulin-like growth factor binding proteins:**

53-90

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**FIGURE 367**

AGACGCTACAGGATGGAGCGGGGCGCAGGAGCCAAGCTGCTGCCGCTGCTGCTGCTTCTG  
CGGGCGACTGGTTTTCACATGTGCACAGACAGATGGCCGGAACGGCTACACGGCGGTCATC  
GAAGTGACCAGCGGGGGTCCCTGGGGCGACTGGGCCTGGCCTGAGATGTGTCCCGATGGA  
TTCTTCGCCAGCGGGTTCTCGCTCAAGGTGGAGCCTCCCCAAGGCATTCTGGCGACGAC  
ACTGCACTGAATGGGATCAGGCTGCACTGCGCGCGCGGGAACGTCCTAGGCAATACGCAC  
GTGGTAGAGTCCCAGTCTGGAAGCTGGGGCGAATGGAGTGAGCCGCTGTGGTGTGCGGGC  
GGCGCCTACCTAGTGGCTTTCTCGCTTCGCGTGGAGGCACCCACGACCCTCGGTGACAAC  
ACAGCAGCGAACAACGTGCGCTTCCGCTGTTCAGACGGCGAGGAACTGCAGGGGCCTGGG  
CTGAGCTGGGGAGACTTTGGAGACTGGAGTGACCATTGCCCAAGGGCGCGTGCGGCCTG  
CAGACCAAGATCCAGGGACCTAGAGGCCTCGGCGATGACACTGCGCTGAACGACGCGCGC  
TTATTCTGCTGCCGCAGTGAACGGCGCCGCCGCCGCGCTCTCTCCCGGGCCAGGAGGC  
TAGTCCCACCTCTTGCTATTAAAGCTTCTCTGAGTTG

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**FIGURE 368**

MERGAGAKLLPLLLLLLRATGFTCAQTDGRNGYTAVIEVTSGGPWGDWAWPEMCPDGFFAS  
GFSLKVEPPQGI PGDDTALNGIRLHCARGNVLGNTHVVESQSGSWGGEWSEPLWCRGGAYL  
VAFSLRVEAPTTLGDNNTAANNVRFRCS DGEELQGPGLSWGDFGDWSDHCPKGACGLQTKI  
QGPRGLGDDTALNDARLFCCRS

**Important features of the protein:**

**Signal peptide:**

1-24

**Transmembrane domain:**

None

**N-myristoylation site:**

41-47

89-95

156-162

**Growth factor and cytokines receptors family signature 2:**

103-110



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**FIGURE 369**

GCCAACTGGCCAAACCTCGGAGACCGTCCTGCGCTCTCTGGAGACGCGCTGTCCGCGC  
CCAGGGTGGTGCCATGTGGGGCGCTCGCCGCTCGTCCGTCTCCTCATCCTGGAACGCCGC  
TTCGCTCCTGCAGCTGCTGCTGGCTGCGCTGCTGGCGGCGGGGGCGAGGGCCAGCGGCGA  
GTACTGCCACGGCTGGCTGGACGCGCAGGGCGTCTGGCGCATCGGCTTCCAGTGTCCCGA  
GCGCTTCGACGGCGGCGACGCCACCATCTGCTGCGGCAGCTGCGCGTTGCGCTACTGCTG  
CTCCAGCGCCGAGGCGCGCCTGGACCAGGGCGGCTGCGACAATGACCGCCAGCAGGGCGC  
TGGCGAGCCTGGCCGGGCGGACAAAGACGGCCCCGACGGCTCGGCAGTGCCCATCTACGT  
GCCGTTCTCATTGTTGGCTCCGTGTTTGTGCGCTTTATCATCTTGGGGTCCCTGGTGGC  
AGCCTGTTGCTGCAGATGTCTCCGGCCTAAGCAGGATCCCCAGCAGAGCCGAGCCCCAGG  
GGGTAAACCGCTTGATGGAGACCATCCCCATGATCCCCAGTGCCAGCACCTCCCGGGGTC  
GTCCTCACGCCAGTCCAGCACAGCTGCCAGTTCAGCTCCAGCGCCAACTCAGGGGCCCG  
GGCGCCCCCAACAAGGTCACAGACCAACTGTTGCTTGCCGGAAGGGACCATGAACAACGT  
GTATGTCAACATGCCCACGAATTTCTCTGTGCTGAACTGTCAGCAGGCCACCCAGATTGT  
GCCACATCAAGGGCAGTATCTGCATCCCCATACGTGGGGTACACGGTGCAGCACGACTC  
TGTGCCCATGACAGCTGTGCCACCTTTCATGGACGGCCTGCAGCCTGGCTACAGGCAGAT  
TCAGTCCCCCTTCCCTCACACCAACAGTGAACAGAAGATGTACCCAGCGGTGACTGTATA  
ACCGAGAGTCACTGGTGGGTTCCTTTACTGAAGGGAGACGAAGGCAGGGGTGGATTTTCG  
AGGTGGAAGT

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**FIGURE 370**

MWGARRSSVSSSWNAASLLQLLLAALLAAGARASGEYCHGWLDAQGVWRIGFQCPERFDG  
GDATICCGSCALRYCCSSAEARLDQGGCDNDRQQGAGEPGRADKDGPDGSAVPIYVPFLI  
VGSVFVAFIILGSLVAACCCRCLRPKQDPQQSRAPGGNRLMETIPMIPSASTSRGSSSRQ  
SSTAASSSSSANS GARAPPTRSQTNCCLPEGTMMNVYVNMPTNFSVLNCQQATQIVPHQG  
QYLHPPYVGyTVQHDSVPMTAVPPFMDGLQPGYRQIQSPFPHTNSEQKMPAVTV

**Important features of the protein:**

**Signal peptide:**

1-33

**Transmembrane domain:**

54-78

**N-glycosylation site:**

223-226

**cAMP- and cGMP-dependent protein kinase phosphorylation site:**

5-8

**N-myristoylation site:**

3-8, 30-35, 60-65, 86-91, 132-137, 211-216, 268-273

**Prokaryotic membrane lipoprotein lipid attachment site:**

128-138

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## FIGURE 371

CACCAGACAGCACTCCAGCACTCTGTTTGGGGGGCATTGAAACAGCAAAATCACTCATA  
AAAGGCCAAAAAATTGCAAAAAAATAGTAATAACCAGCATGGCACTAAATAGACCATGA  
AAAGACATGTGTGTGCAGTATGAAAATTGAGACAGGAAGGCAGAGTGTCTGCTGTGAA  
CCTCAGCTGGGAATGTGCATCAGGCAACTCAAGTTTTTTCACCACGGCATGTGTCTGTGAA  
TGTCCGCAAAACATTCTCTCTCCCCAGCCTTCATGTGTAAACCTGGGGATGATGTGGACC  
TGGGCACTGTGGATGCTCCCTTCACTCTGCAAATTCAGCCTGGCAGCTCTGCCAGCTAAG  
CCTGAGAACATTTCTGTGTCTACTACTATAGGAAAAATTTAACCTGCACTTGGAGTCCA  
GGAAAGGAAACCAGTTATACCCAGTACACAGTTAAGAGAACTTACGCTTTTGGAGAAAAA  
CATGATAATTGTACAACCAATAGTTCTACAAGTGAAAATCGTGCTTCGTGCTCTTTTTTC  
CTTCCAAGAATAACGATCCCAGATAATTATACCATTTGAGGTGGAAGCTGAAAATGGAGAT  
GGTGTAAATTAATCTCATATGACATACTGGAGATTAGAGAACATAGCGAAAACCTGAACCA  
CCTAAGATTTTCCGTGTGAAACCAGTTTTTGGGCATCAAACGAATGATTCAAATTGAATGG  
ATAAAGCCTGAGTTGGCGCCTGTTTCATCTGATTTAAAAATACACACTTCGATTCAGGACA  
GTCAACAGTACCAGCTGGATGGAAGTCAACTTCGCTAAGAACCGTAAGGATAAAAAACCA  
ACGTACAACCTCACGGGGCTGCAGCCTTTTACAGAATATGTCATAGCTCTGCGATGTGCG  
GTCAAGGAGTCAAAGTTCTGGAGTGAAGTGGAGCCAAGAAAAAATGGGAATGACTGAGGAA  
GAAGCTCCATGTGGCCTGGAAGTGTGGAGAGTCTGAAACCAGCTGAGGCGGATGGAAGA  
AGGCCAGTGGGTTGTTATGGAAGAAGGCAAGAGGAGCCCCAGTCCTAGAGAAAAACACTT  
GGCTACAACATATGGTACTATCCAGAAAGCAACACTAACCTCACAGAAACAATGAACACT  
ACTAACCAGCAGCTTGAAGTGCATCTGGGAGGCGAGAGCTTTTGGGTGTCTATGATTTCT  
TATAATTCTCTTGGGAAGTCTCCAGTGGCCACCCTGAGGATTCCAGCTATTCAAGAAAAA  
TCATTTTCAGTGCATTGAGGTCATGCAGGCCTGCGTTGCTGAGGACCAGCTAGTGGTGAAG  
TGGCAAAGCTCTGCTCTAGACGTGAACACTTGGATGATTGAATGGTTTCCGGATGTGGAC  
TCAGAGCCCCACCACCTTTTCTGGGAATCTGTGTCTCAGGCCACGAACCTGGACGATCCAG  
CAAGATAAATTAAAAACCTTTCTGGTGCTATAACATCTCTGTGTATCCAATGTTGCATGAC  
AAAGTTGGCGAGCCATATTCCATCCAGGCTTATGCCAAAGAAGGCGTTCCATCAGAAGGT  
CCTGAGACCAAGGTGGAGAACATTTGGCGTGAAGACGGTCACGATCACATGGAAGAGATT  
CCCAAGAGTGAGAGAAAGGGTATCATCTGCAACTACACCATCTTTTACCAAGCTGAAGGT  
GGAAAAGGATTCTGTAAGCACGCCCATAGCGAAGTGGAAAAAACCCTAAGCCCCAGATA  
GATGCTATGGATAGACCTGTTGTAGGCATGGCTCCCCATCTCATTTGTGACTTGCAACCT  
GGCATGAATCACTTAGCTTCTTTAAATCTCTCTGAAAATGGGGCCAAGAGCACCCACCTT  
TTGGGGTTTTTGGGGTTAAATGAGAGTGAAGTGACAGTACCTGAGAGGAGAGTCTTGAGG  
AAATGGAAGGAGTTGTTATAATTTTGTCCTGGTTAGGCCCTGAATTGACCTCCCGGGAGCT  
CCCCGACCATCATTCCCAGGAATGGCGTGCCTGGCTTAAAGAGTGAGGAGGAACAGACCC  
TGTCACCATGACTTCTACTGCCCCTGCCAAATCATGCTTTTGTTTTTTCAGTCCACCTTAT  
CTCCTGACATCTTAAATACTGGGCAAGGCTTGGATTCTTGCTTAGGCTAAATAATTTTTT  
CTTATGGTAAAAATACACGTAAAAATTTTTTCCAGTTTAAACATTTGAAAGTGTACAATTT  
AGTGGCATTAGAAGCATTCACAATATTGTGCAACCATCACCACTATTTCCAGAACTCTTC  
TATTTCTGCCCAAATAGAAGCCCTATACCATTCATTAGTCACTCCCCATTCTCTCTC  
CCACAGCCCCCTGGCAACTACCAAAGTCTTTGTGTCTCTATGGATTGCCTATTTTGGATA  
TTTCATATACATAGAATCATAAANTAAAAA

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**FIGURE 372**

MCIRQLKFFTTACVCECPQNILSPQPSCVNLGMMWTWALWMLPSLCKFSLAALPAKPENI  
SCVYYYRKNLTCTWSPGKETSYTQYTVKRTYAFGEKHDNCTTNSSTSENRASCSFFLPRI  
TIPDNYTIEVEAENG DGVIKSHMTYWRL ENIAKTEPPKIFRVKPV LGIKRMIQIEWIKPE  
LAPVSSDLKYTLRFRTVNSTSWMEVNF AKNRKDKNQTYNLTGLQP FTEYVIALRC AVKES  
KFWSDWSQEKMGMT EEEAPCGLELWRVLKPAEADGRRPVRL LWKKARGAPVLEKTLGYNI  
WYYPESNTNLTETMNTTNQQLELHLGGESFWVSMISYNSLGKSPVATLRIPAIQEKSFQC  
IEVMQACVAEDQLVVKWQSSALDVNTWMI EWFPD VDSEPTTLSWESVSQATNWTIQQDKL  
KPFWCYNISVYPMLHDKVGEPYSIQAYAKEGVPSEGPETKVENIGVKT V TITWKEIPKSE  
RKGII CNYTIFYQAEGGKGFC KHAHSEVEKNPKPQIDAMDRPVVGMAPP SHCDLQPGMNH  
LASLNLS ENGA KSTHLLGFWGLNESEVTVPERRVLRKWKELL

**Important features of the protein:**

**Signal peptide:**

1-46

**Transmembrane domain:**

None

**N-glycosylation site:**

59-63, 69-73, 99-103, 103-107, 125-129, 198-202, 215-219, 219-223, 309-313, 315-319, 412-416, 427-431, 487-491, 545-549, 563-567

**N-myristoylation site:**

32-38, 137-143, 483-489, 550-556, 561-567

**Amidation site:**

274-278

**Growth factor and cytokines receptors family signature 1:**

62-75

**Fibronectin type III domain:**

54-144

154-247

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**FIGURE 373**

CCAGGTCCAACCTGCACCTCGGTTCTATCGATTGAATTCCTCGGGGATCCTCTAGAGATCC  
CTCGACCTCGACCCACGCGTCCGCCAAGCTGGCCCTGCACGGCTGCAAGGGAGGCTCCTG  
TGGACAGGCCAGGCAGGTGGGCCTCAGGAGGTGCCTCCAGGCGGCCAGTGGGCCTGAGGC  
CCCAGCAAGGGCTAGGGTCCATCTCCAGTCCCAGGACACAGCAGCGGCCACCATGGCCAC  
GCCTGGGCTCCAGCAGCATCAGCAGCCCCCAGGACCGGGGGAGGCACAGGTGGCCCCCAC  
CACCCGGAGGAGCAGCTCCTGCCCCTGTCCGGGGGATGACTGATTCTCCTCCGCCAGGCC  
ACCCAGAGGAGAAGGCCACCCCGCCTGGAGGCACAGGCCATGAGGGGCTCTCAGGAGGTG  
CTGCTGATGTGGCTTCTGGTGTTGGCAGTGGGCGGCACAGAGCACGCCTACCGGCCCGGC  
CGTTAGGGTGTGTGCTGTCCCGGGCTCACGGGGACCCTGTCTCCGAGTCGTTCTGTGCAGC  
GTGTGTACCAGCCCTTCTCACCACCTGCGACGGGCACCGGGCCTGCAGCACCTACCGAA  
CCATTTATAGGACCGCTACCGCCGAGCCCTGGGCTGGCCCTGCCAGGCCTCGCTACG  
CGTGCTGCCCCGGCTGGAAGAGGACCAGCGGGCTTCTGGGGCCTGTGGAGCAGCAATAT  
GCCAGCCGCCATGCCGAACGGAGGGAGCTGTGTCCAGCCTGGCCGCTGCCGCTGCCCTG  
CAGGATGGCGGGGTGACACTTGCCAGTCAGATGTGGATGAATGCAGTGCTAGGAGGGGCG  
GCTGTCCCCAGCGCTGCATCAACACCGCCGGCAGTTACTGGTGCCAGTGTTGGGAGGGGC  
ACAGCCTGTCTGCAGACGGTACACTCTGTGTGCCCAAGGGAGGGCCCCCAGGGTGGCCC  
CCAACCCGACAGGAGTGGACAGTGCAATGAAGGAAGAAGTGCAGAGGCTGCAGTCCAGGG  
TGGACCTGCTGGAGGAGAAGCTGCAGCTGGTGCTGGCCCCACTGCACAGCCTGGCCTCGC  
AGGCACTGGAGCATGGGCTCCCGGACCCCGGCAGCCTCCTGGTGCACTCCTTCCAGCAGC  
TCGGCCGCATCGACTCCCTGAGCGAGCAGATTTCTTCTTCTGGAGGAGCAGCTGGGGTCTT  
GCTCCTGCAAGAAAGACTCGTGACTGCCCAGCGCCCCAGGCTGGACTGAGCCCCCTCACGC  
CGCCCTGCAGCCCCCATGCCCTGCCCAACATGCTGGGGGTCCAGAAGCCACCTCGGGGT  
GACTGAGCGGAAGGCCAGGCAGGGCCTTCTCCTTTTCTCCTCCCCTTCCCTCGGGAGG  
GTCCCCAGACCTGGCATGGGATGGGCTGGGATTTTTTTTGTGAATCCACCCCTGGCTAC  
CCCCACCCTGGTTACCCCAACGGCATCCCAAGGCCAGGTGGGCCCTCAGCTGAGGGAAGG  
TACGAGTTCCCTGCTGGAGCCTGGGACCCATGGCACAGGCCAGGCAGCCCGGAGGCTGG  
GTGGGGCCTCAGTGGGGGCTGCTGCCTGACCCCCAGCACATAAAAATGAAACGTGAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCGCGACTCTAGAGTC  
GACCTGCAGAAGCTTGGCCGCCATGGCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAAT

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**FIGURE 374**

MTDSPPPGHPPEEKATPPGGTGHEGLSGGAADVASGVGSGRHRARLPARPLGCVLSRAHGD  
PVSESFVQRVYQPFLTTCDGHRACSTYRTIYRTAYRRSPGLAPARPRYACCPGWKRTSGL  
PGACGAAICQPPCRNGGSCVQPGRRCPCAGWRGDTQCQSDVDECSARRGGCPQRCINTAGS  
YWCQCWEGHSLSADGTL CVPKGGPPRVAPNPTGVDSAMKEEVQRLQSRVDLLEEKQLVL  
APLHSLASQALEHGLPDPGSLLVHSFQQLGRIDSLSEQISFLEEQLGSCSCKKDS

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FIGURE 375

Wholemount In Situ with PRO1449 Orthologue

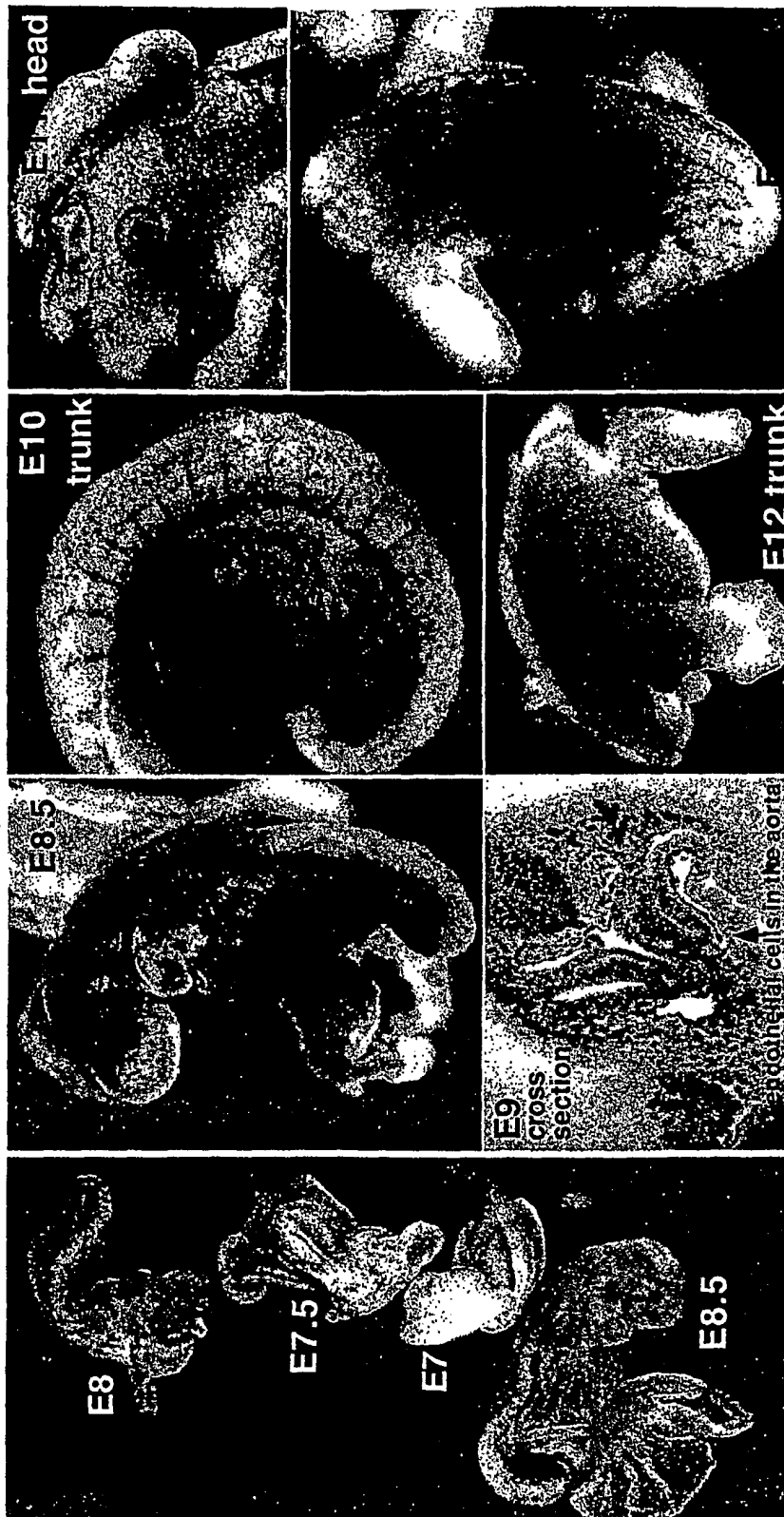
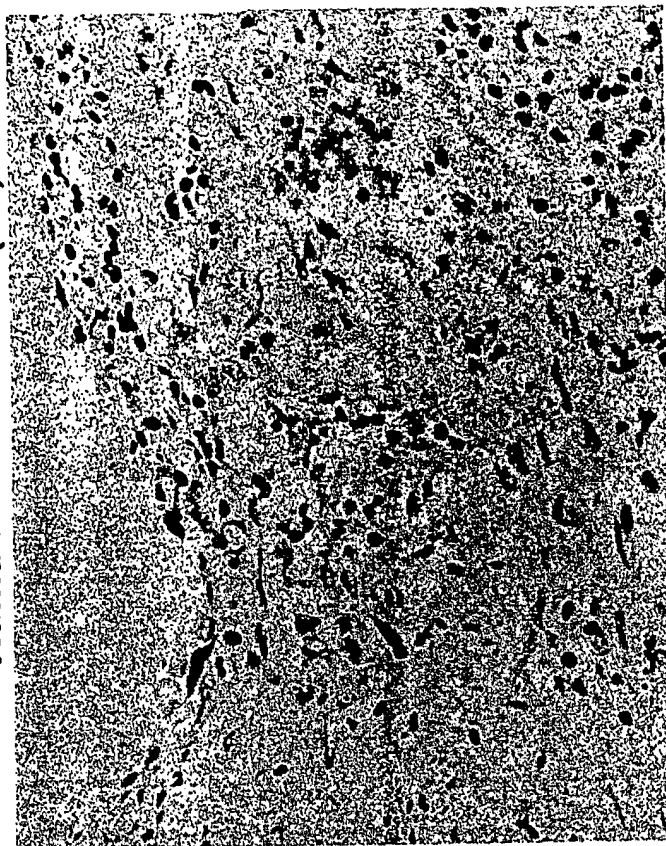


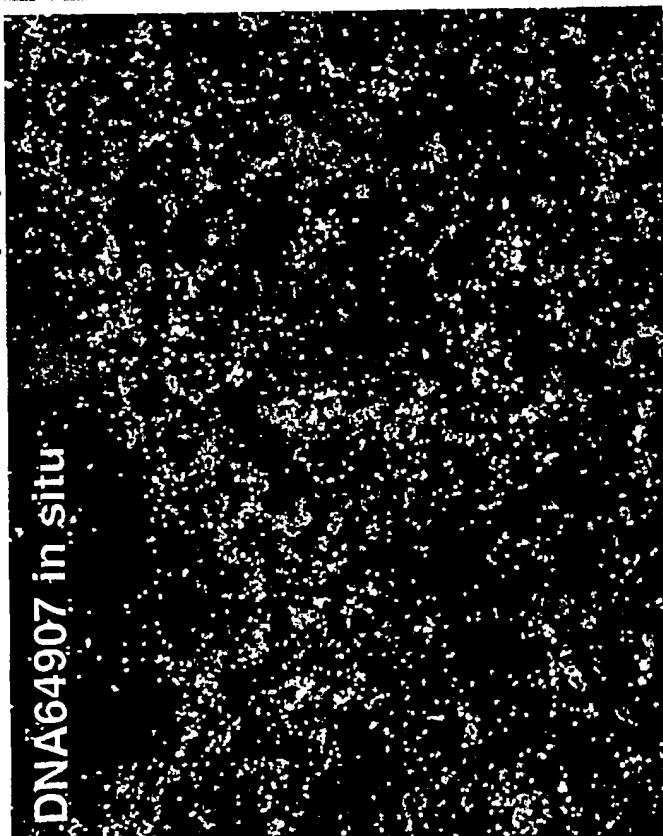
FIGURE 376

PRO1449 is expressed in vasculature of many inflamed and diseased tissues

Human tumor tissue (BF)



Human tumor tissue (DF)



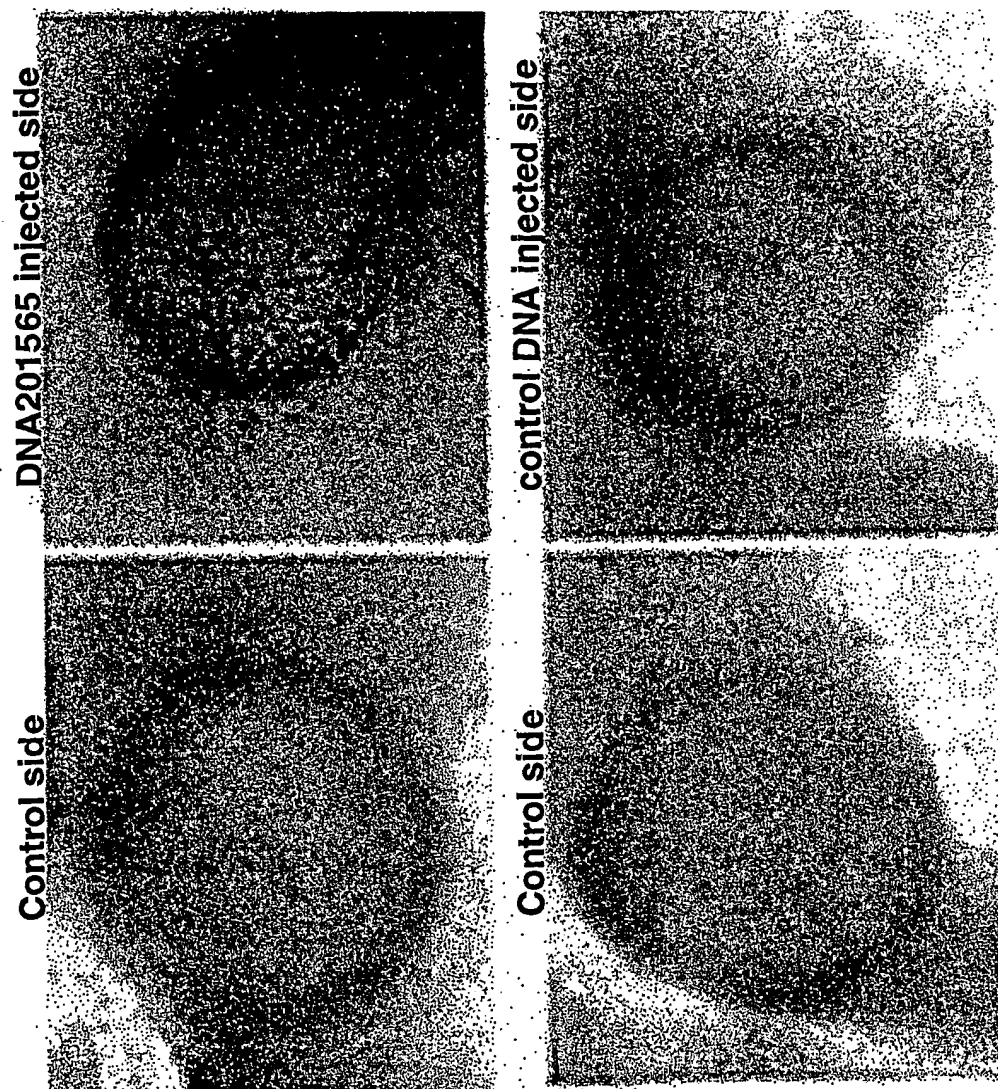
DNA64907 in situ



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**FIGURE 377**

Mouse orthologue of PR01449 induces ectopic vessels in the eyes of chicken embryos



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International Bureau(43) International Publication Date  
3 January 2002 (03.01.2002)

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(51) International Patent Classification <sup>7</sup> : C07K 14/47, C12N 15/12, A61K 38/17, C07K 16/18		09/808,689	14 March 2001 (14.03.2001)	US
		09/816,744	22 March 2001 (22.03.2001)	US
		09/828,366	5 April 2001 (05.04.2001)	US
(21) International Application Number: PCT/US01/19692		09/854,208	10 May 2001 (10.05.2001)	US
		09/854,280	10 May 2001 (10.05.2001)	US
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(30) Priority Data:				
60/213,637	23 June 2000 (23.06.2000)	US	(71) Applicant (for all designated States except US): GENEN- TECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).	
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PCT/US00/23522	23 August 2000 (23.08.2000)	US		
PCT/US00/23328	24 August 2000 (24.08.2000)	US		
60/230,978	7 September 2000 (07.09.2000)	US		
60/000,000	15 September 2000 (15.09.2000)	US	(72) Inventors; and (75) Inventors/Applicants (for US only): BAKER, Kevin, P. [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). FERRARA, Napoleone [US/US]; #704, 2090 Pacific Avenue, San Francisco, CA 94109 (US). GERBER, Hanspeter [CH/US]; #5, 1121 Tennessee Street, San Francisco, CA 94107 (US). GERRITSEN, Mary, E. [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GODOWSKI, Paul, J. [US/US]; 25 Orange Court, Hillsborough, CA 94010 (US). GURNEY, Austin, L. [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). HILLAN, Kenneth, J. [GB/US]; 64 Seward Street, San Francisco, CA 94114 (US). MARSTERS, Scot, A. [US/US]; 990 Cherry Street, San Carlos, CA 94070 (US). PAN, James [CA/US]; 2705 Coronet Boulevard, Belmont, CA 94002 (US). PAONI, Nicholas, F. [US/US]; 1756 Terrace Drive, Belmont, CA 94002 (US). STEPHAN, Jean-Philippe, F. [FR/US]; 320 C Lansdale Avenue, Millbrae, CA 94030 (US). WATAN- ABE, Colin, K. [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). WILLIAMS, P., Mickey [US/US]; 509 Alto Avenue, Half Moon Bay, CA 94019 (US). WOOD, William, I. [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US). YE, Weilan [CN/US]; 119 Barkentine Street, Foster City, CA 94404 (US).	
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PCT/US00/34956	20 December 2000 (20.12.2000)	US		
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PCT/US01/06520	28 February 2001 (28.02.2001)	US		
PCT/US01/06666	1 March 2001 (01.03.2001)	US		
09/802,706	9 March 2001 (09.03.2001)	US		

[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

(57) Abstract: Compositions and methods are disclosed for stimulating or inhibiting angiogenesis and/or cardiovascularization in mammals, including humans. Pharmaceutical compositions are based on polypeptides or antagonists thereto that have been identified for one or more of these uses. Disorders that can be diagnosed, prevented, or treated by the compositions herein include trauma such as wounds, various cancers, and disorders of the vessels including atherosclerosis and cardiac hypertrophy. In addition, the present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

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(74) Agents: AGARWAL, Atulya, R. et al.; c/o GENENTECH, INC., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/19692

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 A61K38/17 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

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X	WO 99 43802 A (KATO SEISHI ;KIMURA TOMOKO (JP); PROTEGENE INC (JP); SEKINE SHINGO) 2 September 1999-(1999-09-02)- see clone HP02239.	1-19
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

21 August 2002

Date of mailing of the international search report

29. 11. 2002

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Smalt, R

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/19692

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No.  
PCT/US 01/19692

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 20-34, 37 and 41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
  
1-35, 37, 41 all partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 20-28,31,34,35,37, and 41 relate to products defined by reference to a desirable characteristic or property, namely having (ant)agonistic activity towards the protein(s) of claim 1. The application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search impossible. Consequently, the search of said claims, in as far as the (ant)agonists are concerned, has been carried out for those aspects which appear to be clear, supported and disclosed, namely those parts relating to antibodies directed against the protein(s) of claim 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: 1-35, 37, 41 all partially

Nucleic acid with at least 80% identity to seq.ID.1 and protein encoded thereby, vector, host cell, method for producing the protein, chimeric protein, antibody, and pharmaceutical compositions.

Inventions 2-187: 1-42, all partially,  
and as far as applicable

Subject matter as defined for invention 1. above, but limited to the respective nucleic acid sequences 3-373 (odd numbers) and the polypeptides encoded thereby (seq.ID's 4-374, even numbers).

For the sake of conciseness, the first subject matter is explicitly defined, the other subject matters are defined by analogy thereto.

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